Studies Towards the Asymmetric Synthesis of Mechanically Planar Chiral Rotaxanes

Pauline Elizabeth Glen

Submitted for the degree of Doctor of Philosophy

Heriot-Watt University

School of Engineering and Physical Sciences

January 2013

Abstract

The work reported in this thesis consists of studies towards the asymmetric synthesis of mechanically planar chiral rotaxanes *via* an asymmetric active template approach. It describes the synthesis of a novel C_1-symmetric bis(oxazoline) macrocycle and the investigation of this C_1-symmetric bis(oxazoline) macrocycle, and other C_1- and C_2-symmetric non-macrocyclic bis(oxazoline)s, as ligands in the Cadiot-Chodkiewicz, oxidative Heck and CuAAC 'click' reactions as part of the study towards the synthesis of asymmetric planar chiral rotaxanes. The thesis is divided into four chapters:

Chapter one is an introduction to rotaxanes and includes an overview of the synthesis of rotaxanes and chirality in rotaxanes.

Chapter two is an account of the synthesis of a novel C_1-symmetric bis(oxazoline) macrocycle.

Chapter three describes the investigation of bis(oxazoline)s, C_1- and C_2-symmetric, macrocyclic and non-macrocyclic, as ligands in the Cadiot-Chodkiewicz, oxidative Heck and CuAAC 'click' reaction.

Chapter four provides a formal report of the experimental procedures.

Acknowledgements

First I would like to thank Ai-Lan for the opportunity of working in the Lee group on this project and for all the help and support you have given me through the process.

Thanks to the members of the Lee group both past and present who have provided help when required and made the lab a fun place to be; to Max, James, Jamie, Paul and Sarah. Special thanks go to James for all his help throughout the project – I do not think I would have got to this point without it.

I would like to thank Mari for everything – the chats, the help, the friendship and the occasional motivational "speech". I could not have done it without you.

I would like to thank all the staff in the chemistry department at Heriot-Watt for all the knowledge they have given me and all the support throughout the nine years I have been here. Thank you to the members of the organic staff who have provided invaluable help through this project and to Dave Ellis and Alan Boyd for their help and discussions on what NMR can and cannot do! Special thanks also go to Christina Graham for all her help and support throughout my time at Heriot-Watt.

Thanks go to the EPSRC for providing the funding for this project.

Last, but not least, a big thank you to my family. Julie you have been amazing; I stayed sane because of you. Mum and Dad, I owe everything to you (including a year's rent). Thanks.

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Contents

Abbreviations

18-crown-6	1,4,7,10,13,16-hexacyclooctadecane
δ	NMR chemical shift
ν	wavenumber
Å	Angstrøm
Ac	acetyl
ambox	amine-bis(oxazoline)
aq.	aqueous
Ar	aryl
BIPY	bypridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Box	bis(oxazoline)
bp	boiling point
BQ	benzoquinone
br.	broad
Bu	butyl
c	concentration
C_1/C_2	symmetry point group
CAM	cerium ammonium molybdate
CB	cucurbituril
cm	centimetre(s)
cm^{-1}	wavenumbers
COD	cycloocta-1,5-diene
conc.	concentration
conv.	conversion
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CuAAC	copper-catalyzed azide-alkyne cycloaddition
d	doublet
dbfbox	dibenzofurandiyl-bis(oxazoline)
DCM	dichloromethane
de	diasteromeric excess
°C	degrees Celsius

deg	degrees
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DHP	dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N* dimethylformamide
DMSO	dimethsulfoxide
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
en	ethylene diamine
EPSRC	Engineering and Physical Sciences Research Council
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
FTIR	Fourier transform infra-red
g	gram(s)
GCCIP	gas chromatography positive chemical ionisation
h	hour(s)
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum coherence
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
^{i}Pr	*iso*-propyl
IR	infra-red
J	NMR coupling constant
lit.	literature value

M	molar (mol/litre)
m	multiplet
Me	methyl
mg	milligrams
MHz	mega Hertz
min(s)	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
m/z	mass/charge ratio
n	*normal*
NBS	*N*-bromosuccinimide
nm	nanometre(s)
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
p	*para*
Pd/C	palladium on activated charcoal
Ph	phenyl
phebox	phenol-bis(oxazoline)
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
pybox	pyridine-bis(oxazoline)
q	quartet
quin.	quintet
R	undefined alkyl or aryl group
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
t	triplet
t	*tertiary*

tert	*tertiary*
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
^{t}Bu	*tert*-butyl
temp.	temperature
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*para*-toluene sulfonate (tosyl)
UV	ultraviolet
wrt	with respect to
w/w	weight/weight

Chapter 1
Introduction

Chapter 1: Introduction

1.1. Mechanically Interlocked Structures

Entanglement of one or more components without the use of chemical bonds produces a mechanically interlocked structure (Figure 1.1).[1] These topologically connected species are held together *via* a *mechanical* bond which cannot be undone without the breaking of chemical bonds. These unusual structures are of interest to chemistry, both as curiosities and due to their potential as molecular machines.[1] Mechanically interlocked structures are also found in biological systems; in DNA structures[2, 3] and proteins.[4-6] There are a range of reviews in the literature on the topic of these entangled systems, highlighting the interest in this field.[7-20]

Figure 1.1. Representation of mechanically interlocked structures: **A** - prime knot (trefoil knot); **B** - composite knot (catenane); **C** - [2]rotaxane.

Whilst both composite molecular knots and rotaxanes consist of two components held together *via* mechanical bonds, they are fundamentally different. Composite molecular knots, of which catenanes are the simplest, are topological isomers of their non-interlocked components; *i.e.* they are chemically identical but are topologically different and the two isomers cannot be inter-converted without breaking chemical bonds (a, Figure 1.2).[1] Rotaxanes consist of a macrocycle (*rota*) threaded onto an axle/thread (*axis*) which terminates in stopper groups too bulky to pass through the macrocycle cavity, capturing it on the axle (**C**, Figure 1.1). In theory, rotaxanes can be converted into their constituent parts by infinitely expanding the ring to pass over the stopper groups and they are therefore not topological isomers (b, Figure 1.2). However, in reality this is not usually possible, and rotaxanes are classed as topologically connected species.[21]

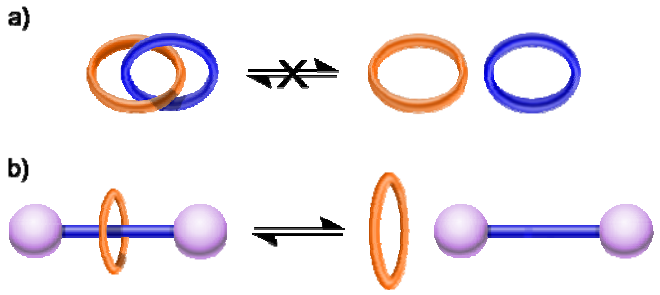


Figure 1.2. Topological isomers. a) Catenanes cannot be inter-converted with their composite rings without breaking chemical bonds. b) Rotaxanes can, in theory, convert to their axle and ring without breaking chemical bonds by expansion of the macrocycle.[21]

Rotaxanes are classified according to the number of separate components that comprise the structure; *i.e.* a [2]rotaxane consists of one macrocycle and one axle, a [3]rotaxane has either one axle and two macrocycles or one macrocycle and two axles, *etc* (**A-C**, Figure 1.3).[22] Rotaxanes with more unusual conformations have also been synthesised, such as: branched and side-chain variations;[23, 24] rotaxanes with linked macrocycles, either internally (bonnanes)[25] or externally to form polyrotaxanes;[26] a [3]rotacatenane;[27] and higher order rotaxanes, such as [7]rotaxanes (**D-H**, Figure 1.3).[28] Linking of rotaxanes has also lead to rotaxane supramolecular organic frameworks (RSOFs)[29-31] and a rotaxane linked block copolymer has also been synthesised.[32]

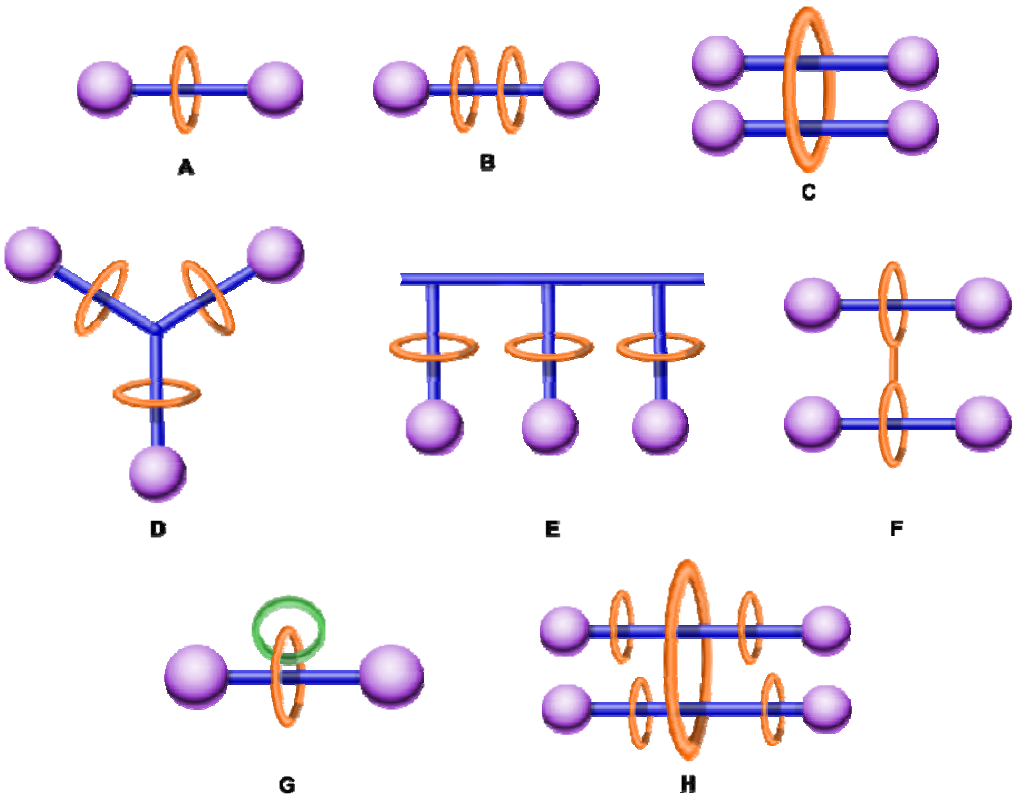


Figure 1.3. Rotaxane structures. [2]rotaxane (**A**); [3]rotaxanes (**B** and **C**); branched rotaxane (**D**); side-chain rotaxane (**E**); bonnane (**F**); [3]rotocatenane (**G**) and a [7]rotaxane (**H**).

1.2. Applications of Rotaxanes

Rotaxanes have found applications in various different fields; namely as molecular machines and sensors, but also in asymmetric catalysis and other areas, such as medicine, where rotaxanes could be utilised as cytotoxic agents.[33]

1.2.1. Molecular Machines

Mechanically interlocked structures have excited interest due to their possible use as molecular machines. Molecular machines are assemblies of molecular components which, under external stimuli, can move to perform specific tasks.[34] Many of these molecular machines can be described by their analogues in the macroscopic world in terms of the mechanical motion undertaken by the device. Hence, a molecular switch can be seen as one component moving controllably between two or more points relative to another component of the device, influencing the system by its position (Figure 1.4).[35] The very nature of mechanically interlocked structures makes them ideal candidates for the basis of molecular machines. The ability of the separate components in catenanes and rotaxanes to move relative to one another, but still be restricted enough in that movement for it to be controllable, has resulted in these structures having a central role in this field.[15, 35-42]

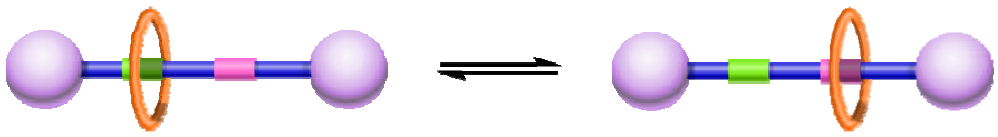
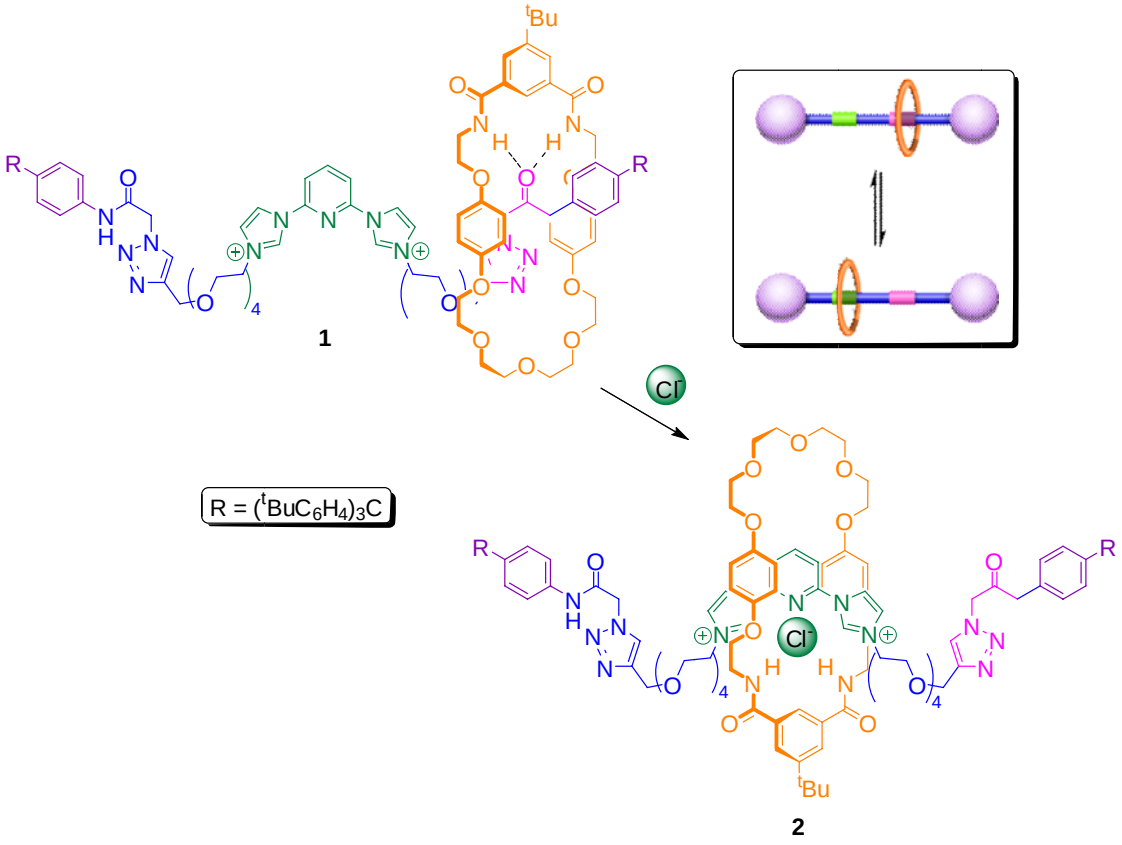


Figure 1.4. Rotaxane switch.

Rotaxanes have been investigated extensively in the field of molecular machines; particularly as molecular switches and shuttles due to the free movement of the macrocycle along the axle. By introducing 'stopping points' along the thread, *via* recognition sites, the macrocycle can be induced to shuttle or switch between these points, depending on external stimuli (Scheme 1.1). The rate of shuttling between two sites can be controlled by temperature and solvent among other things.[43-49] Switching between one recognition site and another in a controlled fashion can be induced by a range of external stimuli, including light,[50-53] pH,[49, 54-58] metal centres,[59] ions[60-62] and the reduction/oxidation of various centres in the system.[50, 63-70]



Scheme 1.1. Switching of a macrocycle between sites on an axle induced by addition of an anion; rotaxane **1** to rotaxane **2**.[61]

Although switches and shuttles are the most common type of rotaxane molecular machines, rotaxanes have been utilised in other molecular devices. The rotation of the macrocycle around the axle can be controlled to give pirouetting rotaxanes (a, Figure 1.5).[71-74] Rotaxanes have also been used as the basis for molecular muscles/springs (b, Figure 1.5)[38, 75, 76] and pistons (c, Figure 1.5),[77] utilising the translational motion of the macrocycle along the axle, but tying the movement to a larger structure.

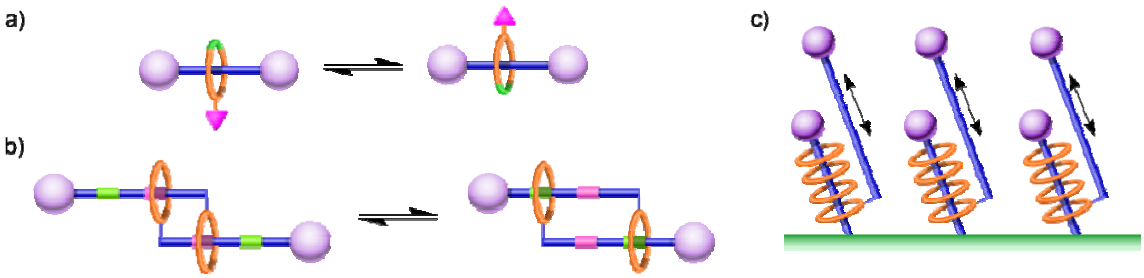
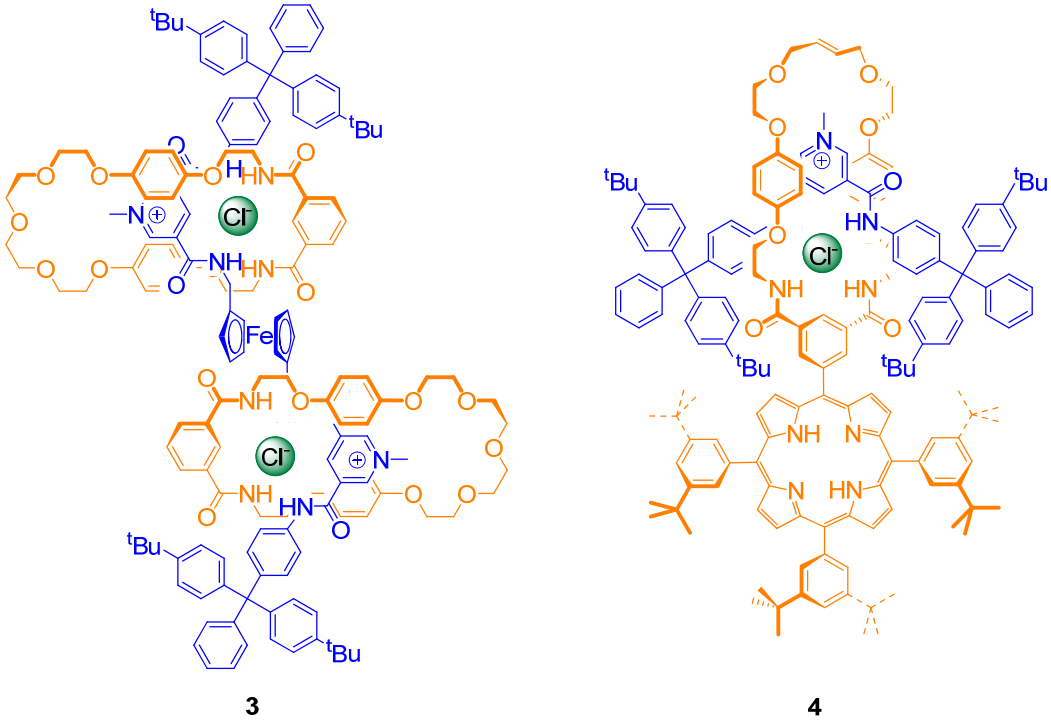


Figure 1.5. Rotaxane molecular machines. a) Pirouetting rotaxanes. b) Molecular muscles/springs. c) Rotaxane piston anchored to a surface.

1.2.2. Molecular Sensors

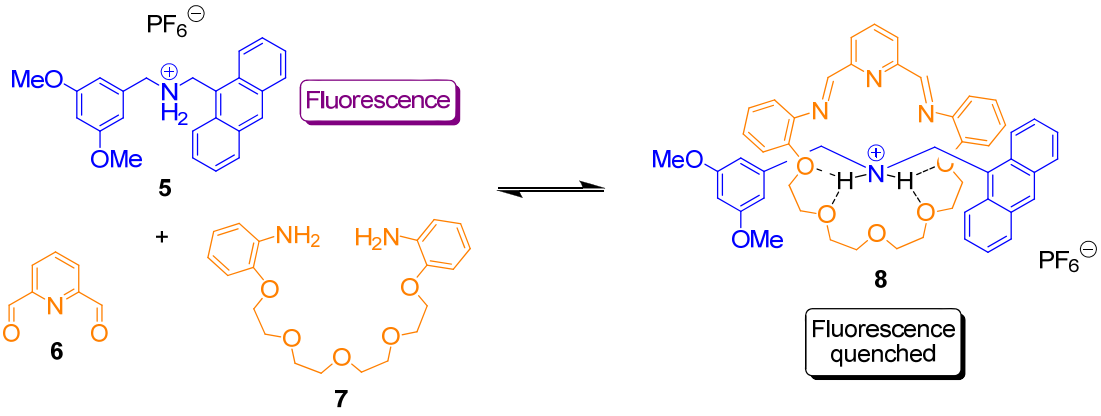
As well as their usage in the field of molecular machines, rotaxanes have also found a place as molecular sensors. Rotaxanes can be designed with receptor points for a range of different species, such as metal cations[78] and halogens,[79] and they can be 'sensed' in a variety of different ways. Beer and co-workers have developed rotaxane electrochemical sensors, where the binding of an anion affects the redox pathway of the rotaxane system. They have utilised both ferrocene- and porphyrin-functionalised rotaxanes in the sensing of halogen and sulfate ions (Figure 1.6).[80-82]



3 **4**

Figure 1.6. Electrochemical rotaxane sensors for chloride ions. Ferrocene-containing [3]rotaxane **3**[80] and porphyrin-containing [2]rotaxane **4**.[82]

Fluorescence of rotaxanes has also been used as a means of detecting the presence of different chemical species. Stoddart *et al.* developed a system in which the self-assembly of a rotaxane from its constituent parts was a reversible process (Scheme 1.2).[83] The position of the equilibrium between rotaxane **8** and its individual components, **5**, **6** and **7**, could be affected by the conditions, namely the presence of water or acid. When the anthracene component **5** was isolated fluorescence was observed and when the anthracene moiety was within the rotaxane structure the fluorescence was quenched. Hence, it was possible to detect the presence of acid, and even the relative concentration of acid between samples, by observing the intensity of fluorescence from the sample.



Scheme 1.2. Rotaxane self-assembly equilibrium affected by acid concentration. Fluorescence of axle quenched by hydrogen bonding in rotaxane.[83]

Rotaxanes have also been used to enantioselectively detect amino acid derivatives. Kameta and Hiratani synthesised a racemic mixture of mechanically planar chiral rotaxanes, **9** and **10**, and used them to bind selectively to phenylalaninol: one enantiomer bound selectively to D-phenylalaninol, the other to the L-form, due to the chiral cavity produced between the axle and macrocycle components of the rotaxane (Figure 1.7).[84]

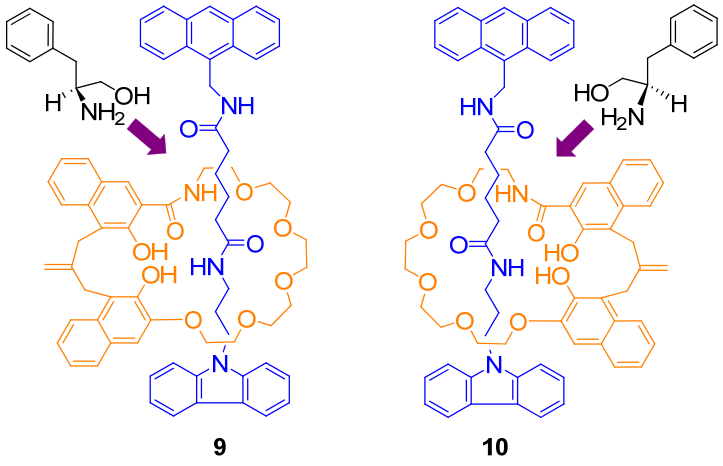


Figure 1.7. Sensing chirality in amino acid derivatives.[84]

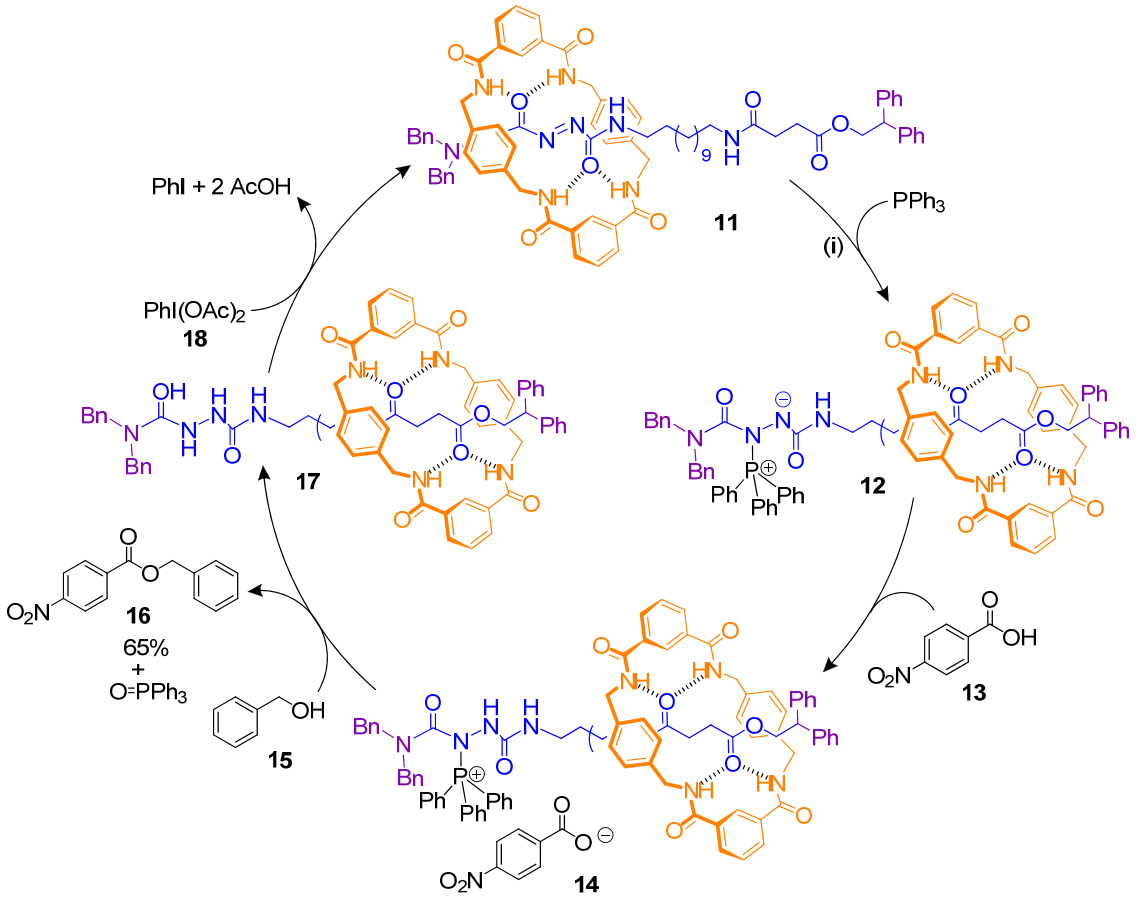
1.2.3. Catalysis

A much less developed field in the application of rotaxanes is their use in catalysis. They can be used as organocatalysts in their own right, or as ligands in metal-catalysed reactions. The mechanically interlocked structure of rotaxanes can provide unique opportunities in the field of catalysis.

Organocatalysts

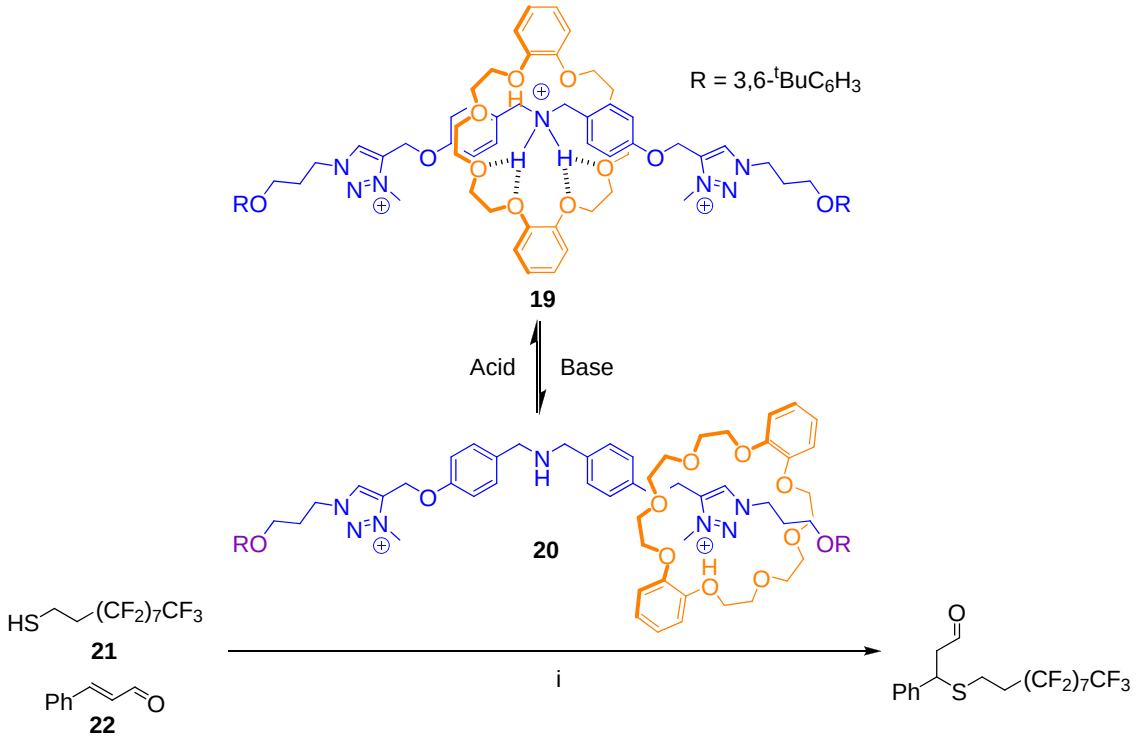
Rotaxanes can be synthesised with a variety of different functional groups present on both the wheel or axle components, thus providing a wide range of possibilities for their use as organocatalysts. However, only a few examples of the application of rotaxanes as organocatalysts exist in the literature.

Berná and co-workers prepared a rotaxane containing an azodicarboxamide group on the axle, **11**, which, when treated with triphenylphosphine, catalyses the Mitsunobu esterification of 4-nitrobenzoic acid, **13**, with benzylic alcohol, **15** in a 65% yield (Scheme 1.3).[85] The reaction results in the production of the hydrazo derivative of rotaxane **11**, **17**, which can be oxidised back to rotaxane **11** with iodosobenzene diacetate **18**. Thus, the conversion of acid **13** to ester **16** results in the shuttling between rotaxanes **12** and **11** due to the different binding ability between the macrocycle and different thread components in different oxidation states.



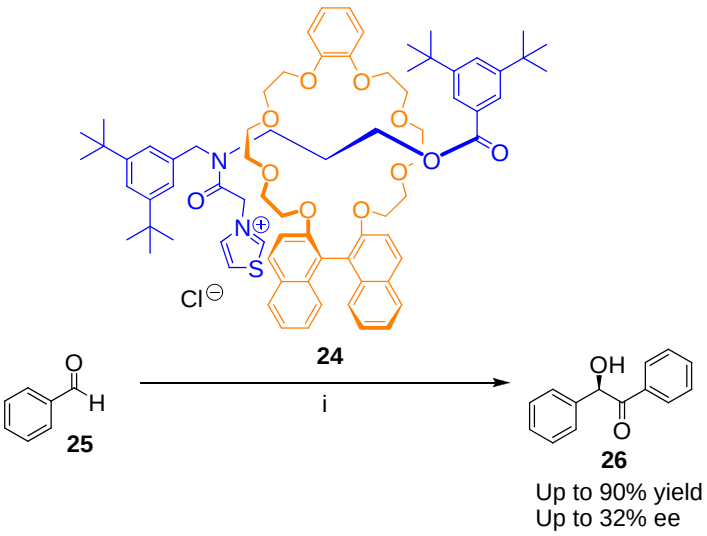
Scheme 1.3. Mitsunobu esterification of acid **13** with alcohol **15** catalysed by rotaxane **11**. Reagents and conditions: (i) **11** (10 mol%), CH_3CN, 50 °C.[85]

Leigh *et al.* also produced a switchable rotaxane organocatalyst.[86] In this case, the switching of the macrocycle between different points on the axle determined the ability of the rotaxane to catalyse the reaction rather than being a product of that reaction. At high pH, the amine group on the thread is a poorer receptor for the macrocycle than the triazolium rings, and rotaxane **20** is formed, which can catalyse the Michael addition of an aliphatic thiol, **21**, to *trans*-cinnamaldehyde, **22**, *via* imminium formation with an 83% yield (Scheme 1.4). When the pH is lowered, the ammonium group thus formed is a much better receptor for the macrocycle than the triazolium rings, and so rotaxane **19** is formed, which cannot catalyse the Michael addition reaction as the macrocycle blocks the approach of the reactants to the ammonium group (Scheme 1.4).



Scheme 1.4. Michael addition of thiol **21** to *trans*-cinnamaldehyde **22** catalysed by rotaxane **20**. Reagents and conditions: (i) **20**·2PF_6 (5 mol%), DCM, RT.[86]

Unsymmetrical rotaxanes can provide a unique chiral transfer field through non-covalent bonding based on the chemical field created between the wheel and axle components.[87] Takata *et al.* were the first to employ chiral rotaxanes in an enantioselective reaction (Scheme 1.5).[88, 89] Rotaxane **24** catalysed the benzoin condensation of benzaldehyde **25** with yields up to 90% and with up to 32% ee by utilising *through space* transfer of the axial chirality of the macrocycle to the catalytic achiral thiazolium moiety on the axle.



Scheme 1.5. Benzoin condensation of benzaldehyde **25** catalysed by rotaxane **24**. Reagents and conditions: (i) **24** (5-10 mol%), Et_3N, MeOH, -20 → 30 °C.[88]

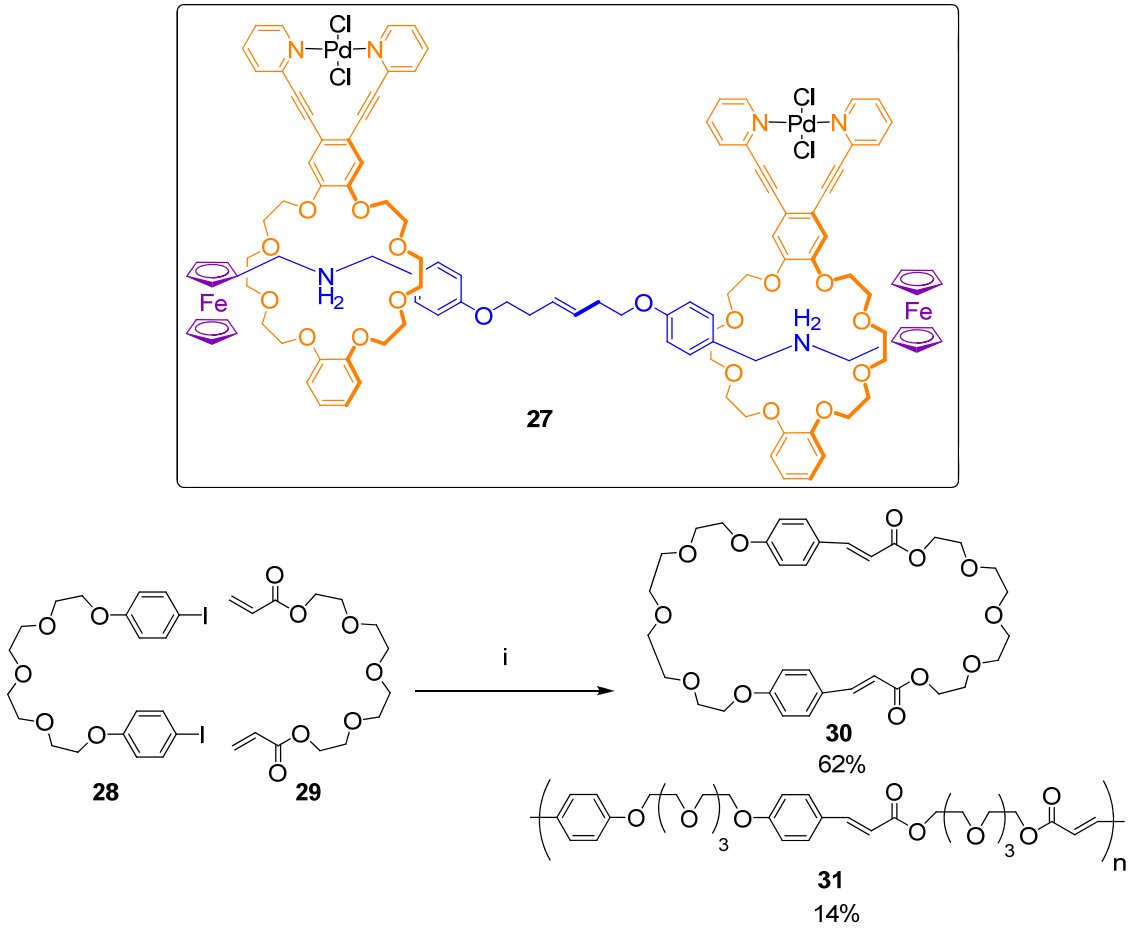
Ligands in Metal-Catalysed Reactions

The use of rotaxanes in catalysis also extends to their employment as novel ligands in metal-catalysed reactions. As a variety of metals are used in the synthesis of rotaxanes through metal template methods, there are a range of possibilities for rotaxanes to be used as ligands in metal-catalysed reactions. However, as with their use as organocatalysts, this application of rotaxanes is vastly underdeveloped.

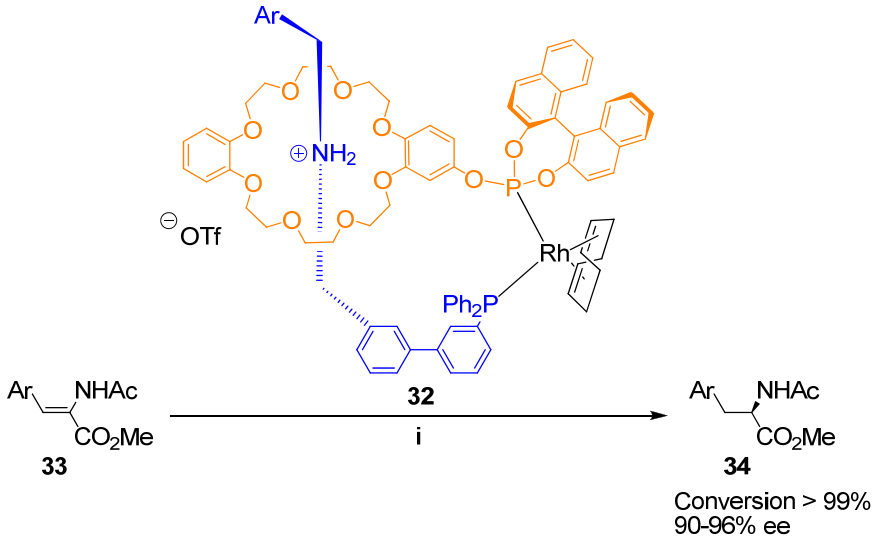
Osakada and co-workers developed a [3]rotaxane, **27**, which could bind two palladium species, one with each macrocycle, to produce a catalyst for the Heck reaction of a diiodobenzene, **28**, with a diacrylate, **29** (Scheme 1.6).[90] The rotaxane was able to enhance the synthesis of the cyclic product, **30**, over the linear **31** (62%:14%) due to the rigidity of the rotaxane structure and the presence of two catalytic sites in close proximity.

The potential of rotaxanes as chiral ligands in asymmetric catalysis was explored by Nishibayashi and co-workers. They utilised a pseudorotaxane-based chelating bidentate ligand in the successful enantioselective rhodium-catalysed hydrogenation of enamides, **33** (Scheme 1.7).[91] When the "lassoed" pseudorotaxane **32** was employed as ligand, the reaction proceeded with both high conversions (> 99%) and high enantioselectivities (90% ee) compared with the use of the crown ether macrocycle component alone (34%

conversion, 71% ee). Fan *et al.* reported a similar system for the reaction, with comparable yields and slightly lower enantioselectivities (> 99% yield, 84% ee).[92]



Scheme 1.6. Heck reaction of diiodobenzene **28** with diacrylate **29** catalysed by rotaxane **27**. Reagents and conditions: (i) Et_3N, **27**·2PF_6 (1 mol%), DMF, 100 °C.[90]



Scheme 1.7. Hydrogenation of enamide **33** catalysed by pseudorotaxane **32**. Reagents and conditions: (i) $[Rh(COD)_2]PF_6$ (1 mol%), **32** (prepared *in situ*, 1 mol%), H_2, DCM, 25 °C.[91]

1.3. Synthesis of Rotaxanes

1.3.1. General Approaches

Overall, there are five general approaches to the synthesis of rotaxanes (Figure 1.8): slipping, threading, trapping, clipping and the use of an active template, which will be discussed later (Section 1.3.6, Pg. 26).[17, 21]

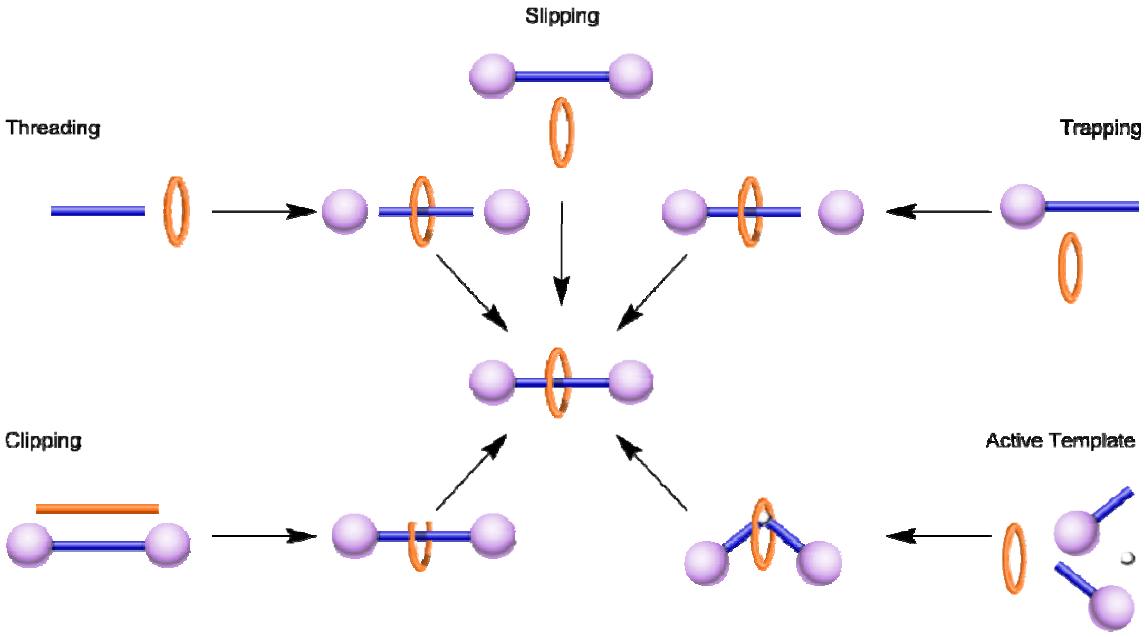


Figure 1.8. General methods for rotaxane synthesis.

Slipping

Slipping involves the threading of a macrocycle onto a pre-stoppered axle (Figure 1.8). It is made possible due to a short-lived increase in the diameter of the macrocycle, usually achieved by elevated temperatures;[93] although Chiu and co-workers employed photoextrusion to reduce the number of atoms within the macrocycle after threading onto the stoppered axle.[94] Due to the nature of the slipping method the process is reversible and it is difficult to distinguish between the point where the product is a rotaxane, with the macrocycle unable to pass over the stopper, and where it is a pseudorotaxane, which can freely dissociate into its component parts.[10]

Threading/Trapping

Threading/trapping is one of the most common methods for the production of rotaxanes. Synthesis of rotaxanes *via* the threading process involves, as the name suggests, the axle component being threaded through the macrocycle to produce a pseudorotaxane, which is then stoppered to yield the rotaxane (Figure 1.8). If the axle is pre-stoppered at one end, the process is termed trapping (Figure 1.8).[1]

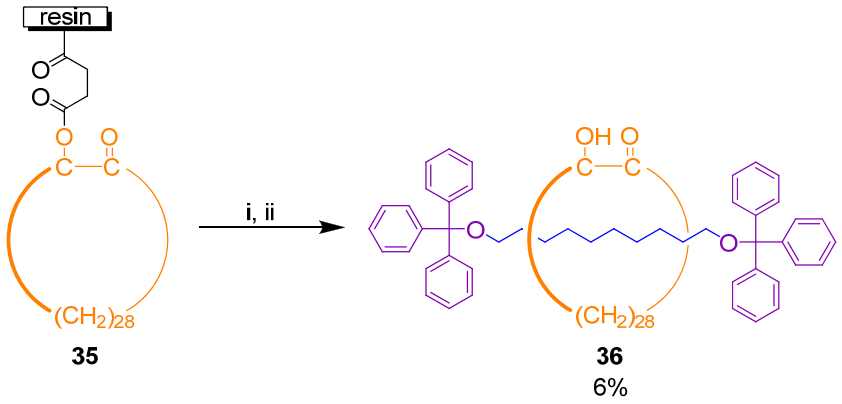
Clipping

Contrary to the threading and slipping methods, where the macrocycle is fully formed before the process begins, the clipping method starts with two linear components. These components are initially held together by intermolecular forces, then cyclisation of one results in the formation of a rotaxane (Figure 1.8).[21] If both linear components were to cyclise the result would be a catenane. The clipping reaction can involve the construction of the macrocycle around either a pre-stoppered axle component, resulting in a rotaxane, or around a 'free' linear component to produce a pseudorotaxane. This pseudorotaxane can then be stoppered to produce the rotaxane.

Rotaxanes can be synthesised from these general methods either by a template or a non-template, statistical process. The templates can take many forms, such as covalent bonds, intermolecular interactions and metal centres.

1.3.2. Statistical Synthesis

The first interlocked molecular architectures were formed *via* statistical threading, where no template is used.[95, 96] This is the simplest mechanism for preparation and is based on the statistical probability that a linear molecule will thread itself though a macrocycle, without any particular intermolecular attractions to aid the process.[10] As such, statistical threading as a process for the synthesis of catenanes and rotaxanes is both unreliable and low yielding. This is exemplified in one of the first reported synthesis of rotaxanes, where Harrison and Harrison used statistical threading of a resin-bound macrocycle, **35**, resulting in only a 6% yield of [2]rotaxane **36** after 70 treatments with the axle and stopper components (Scheme 1.8).[96]



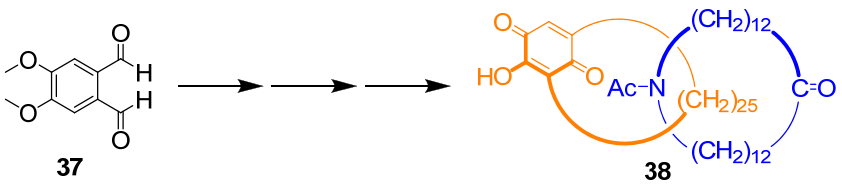
Scheme 1.8. Statistical synthesis of rotaxane **36**. Reagents and conditions: (i) decane-1,10-diol, triphenylmethyl chloride, pyridine, DMF, toluene, 70 repeats; (ii) $NaHCO_3$, MeOH, reflux.[96]

1.3.3. Template Synthesis – Self-Templated Synthesis

The logical improvement to statistical threading was to use some form of molecular interaction to guide the threading process. This templating process would anchor the thread and macrocycle together before stoppering. The introduction of an interaction between the two components would provide a driving force for the rotaxane synthesis. An assortment of intermolecular interactions, such as hydrogen bonds, hydrophobic interactions and π-donor/acceptor interactions, as well as covalent bonds, has been employed to facilitate the synthesis of rotaxanes.

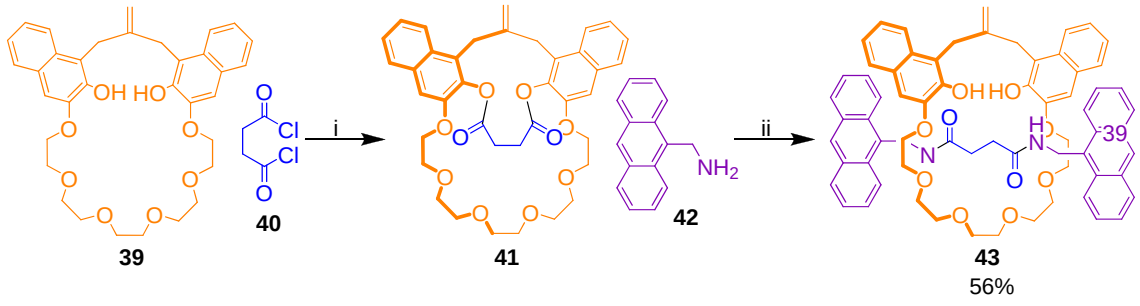
Covalent Bonds

Molecules with a suitably arranged molecular skeleton can be used as templates for the synthesis of mechanically interlocked structures, with the covalent bonds between the different components cleaved after the final connection is made to produce a mechanically bound species. The first description of a template method for the synthesis of a mechanically interlocked structure used covalent bonding as its template.[97] Schill and Lüttringhaus describe the production of catenane **38** through a long series of reactions from 4,5-dimethoxyphthalaldehyde **37** (Scheme 1.9).



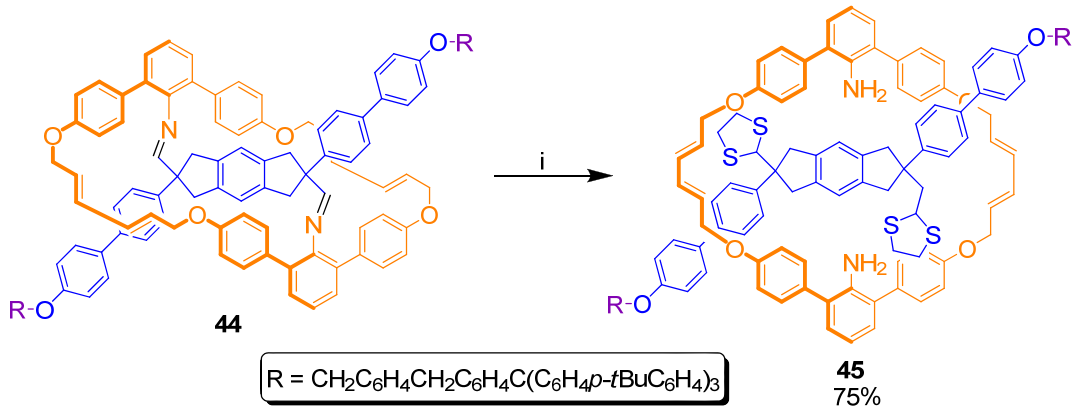
Scheme 1.9. Preparation of catenane **38** *via* a covalent bond template.[97]

Hiratani and co-workers developed a much shorter covalent bond template for the synthesis of rotaxanes.[98] A macrocycle functionalised with phenol groups, **39**, undergoes a diesterification with diacid chloride **40**, to produce the covalently-bound threaded macrocycle **41** (Scheme 1.10). Double aminolysis with amine stopper group **42** then produces rotaxane **43** in a 56% yield. Hiratani *et al.* have utilised this template synthesis method to produce chiral rotaxanes[84, 99] and [3]rotaxanes[100] and Hirose and co-workers have also synthesised a [2]rotaxane in an 82% yield from a modification of the technique.[101]



Scheme 1.10. Covalent bond template synthesis of rotaxane **43**. Reagents and conditions: (i) *t*-BuOK, THF, RT; (ii) DMF 50 °C → 100 °C.[98]

Kawai *et al.* utilised the formation of imine bonds to produce a covalently-bound pre-rotaxane, **44**.[102] Once formed, hydrolysis followed by thioacetalisation removes the covalent bonds and forms rotaxane **45** in a 75% yield (Scheme 1.11).



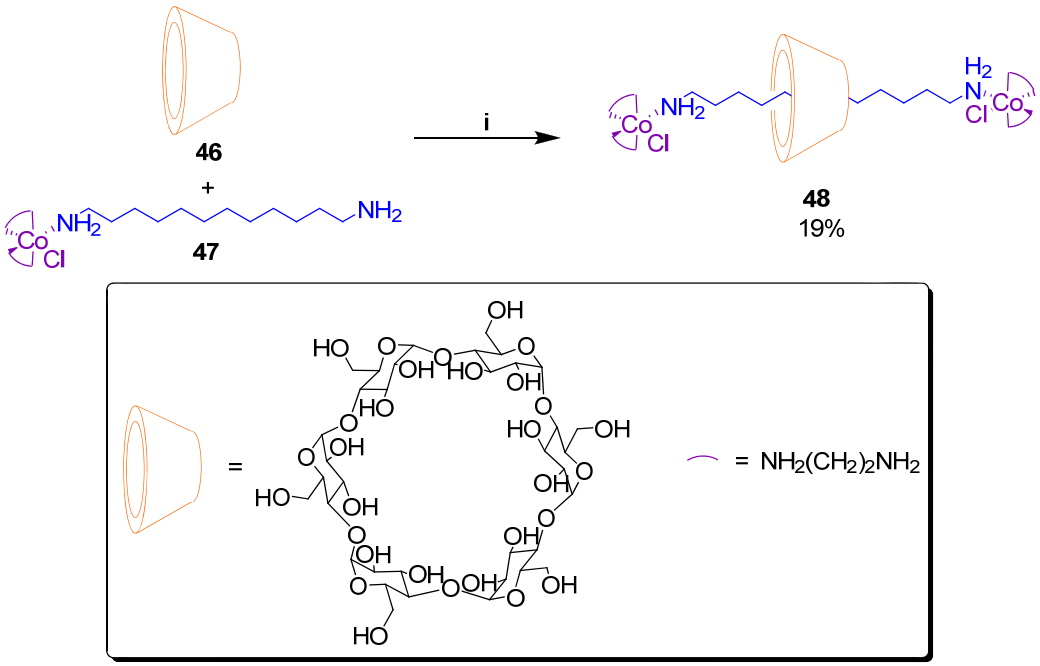
Scheme 1.11. Imine bond template synthesis of rotaxane **45**. Reagents and conditions: (i) TFA, $(CH_2SH)_2$, H_2O, $CHCl_3$, argon, 40 °C.[102]

Hydrophobic Interactions

Pseudorotaxanes can be viewed as simply host-guest complexes, with the axle the guest to the macrocycle host. Both cyclodextrins and cucurbiturils are macrocyclic species which combine a hydrophobic non-polar, hollow interior with a hydrophilic, polar exterior, and are thus capable of forming host-guest complexes based on hydrophobic interactions. Capping of these host-complexes complexes leads to the formation of rotaxanes *via* the threading process.

Cyclodextrins are cyclic oligosaccharides consisting of 6-8 glucose units with the hydroxyl groups presented on the outside of the cone (**46**, Scheme 1.12).[93] They form inclusion complexes with a variety of compounds, such as linear alkyl and aromatic chains, and are popular in the synthesis of rotaxanes.[37, 103, 104]

Ogino and co-workers synthesised the first cyclodextrin rotaxane by threading an α-cyclodextrin **46**, containing six glucose units, with 1,12-diaminododecane, stoppered at one end with $[CoCl(en)_2]$, **47** to form a pseudorotaxane.[105] This was subsequently treated with $[CoCl(en)_2]$ to form rotaxane **48** in a 19% yield (Scheme 1.12); high yielding compared to the statistical threading methods used previously.[96]

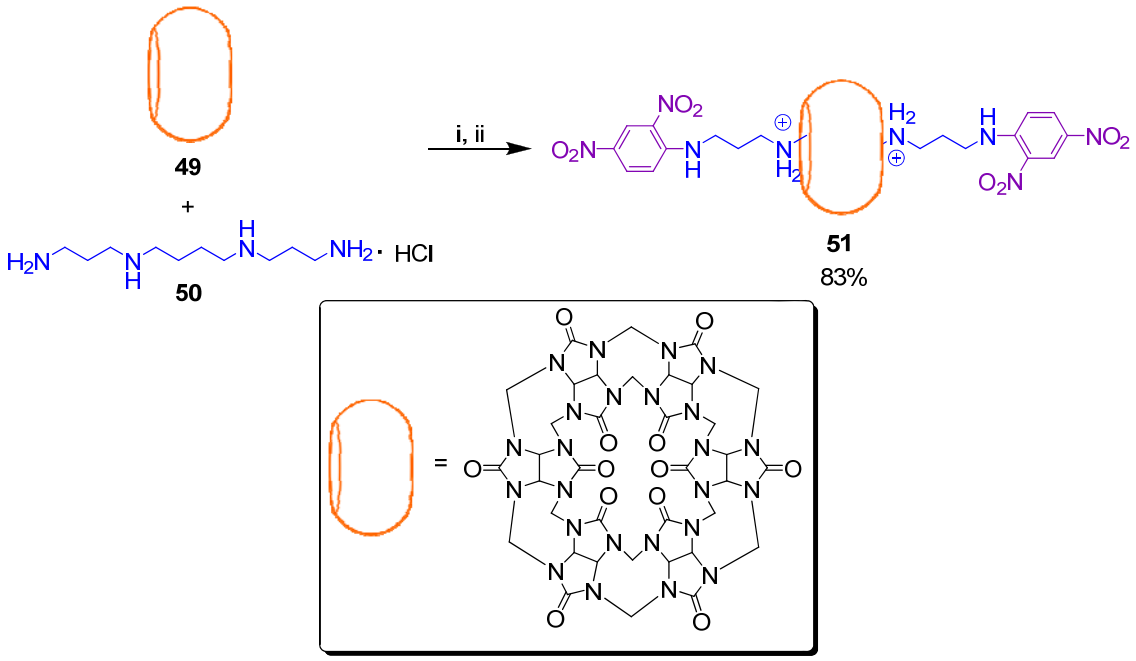


Scheme 1.12. Preparation of the first cyclodextrin-containing rotaxane **48**. Reagents and conditions: (i) *cis*-$[CoCl_2(en)_2]Cl$, DMSO, 75 °C. [105]

Cyclodextrin rotaxanes with a variety of different axles have been synthesised with the alkyl axle functionalised with amide groups;[45] tetrathiafulvalene and triazole;[65] and pyridinium ions[106] to name a few. The cyclodextrin also provides opportunity for functionalisation, such as the addition of a pendant pyridine group.[107]

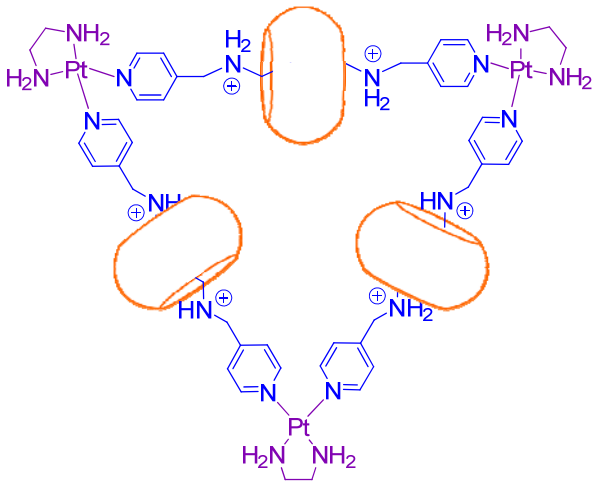
Cucurbiturils, of which cucurbit[6]uril (CB[6]) **49** is the most common, are macrocycles composed of glycoluril units and methylene bridges.[108] They are pumpkin-shaped, from which their name derives, with a hollow, hydrophobic centre with carbonyl groups surrounding the portals at either end. Cucurbiturils prefer positively-charged to neutral guests due to the effect of the carbonyl groups, which allow for charge-dipole interactions.[109] The various different sizes of cucurbiturils available allow a variety of different guests to be bound inside the cavity, with protonated alkyl and aromatic amines being most common.[108, 109]

The first cucurbituril-based rotaxane was synthesised by Kim *et al.* in 1996.[110] Cucurbit[6]uril, **49**, was threaded onto spermine tetrachloride, **50**, then stoppered with dinitrophenol groups (Scheme 1.13). Cucurbituril rotaxane **51** was synthesised in a very high yield of 83%, and was analysed by X-ray crystallography.



Scheme 1.13. Synthesis of CB[6] rotaxane **51**. Reagents and conditions: (i) H_2O; (ii) 2,6-lutidine, 2,4-dinitrofluorobenzene, H_2O, argon.[110]

Cucurbiturils have also been used to synthesise more unusual rotaxanes. These include [4]rotaxanes,[111] polyrotaxanes,[112] paramagnetic rotaxanes[113] and molecular necklaces (Figure 1.9).[114]



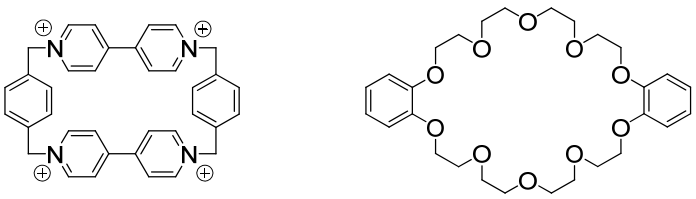
52

Figure 1.9. Cucurbituril-based molecular necklace **52**.[114]

π-electron Donor/Acceptor Interactions

Inclusion complexes are not limited to those based on hydrophobic interactions. Another intermolecular force utilised in the formation of host-guest complexes is that between a π-electron donor and a π-electron acceptor.[115] Stoddart developed the use of these interactions as templates in the formation of mechanically interlocked architectures.[116]

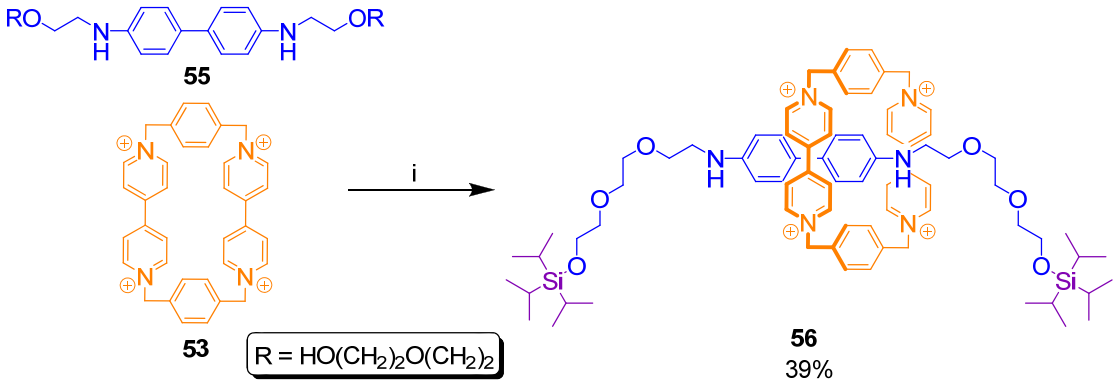
The methodology requires that one of the components involved in the template be a π-electron donor and the other a π-electron acceptor. However, it is inconsequential which of the components is which. Cyclobis(paraquat-*p*-phenylene) **53** (Figure 1.10), a tetracationic cyclophane, is a common electron-poor macrocycle, which will form inclusion complexes with suitable electron rich moieties on the thread component.[116] π-electron rich macrocycles are often aromatic crown ethers, such as dibenzo-30-crown-10 **54** (Figure 1.10), which will interact with π-electron acceptors such as 4,4'-dimethylbipyridinium.[93]



53 **54**

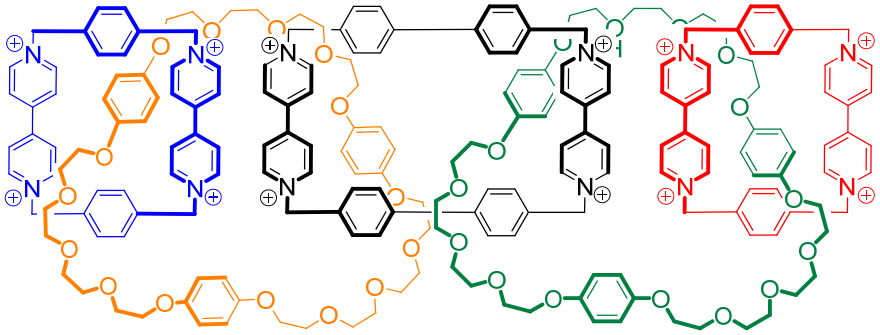
Figure 1.10. π-electron acceptor macrocycle cyclobis(paraquat-p-phenylene) **53** and π-electron donor macrocycle dibenzo-30-crown-10 **54**.

Stoddart used these π-electron donor/acceptor systems in the synthesis of rotaxanes. A general example is the use of cyclobis(paraquat-p-phenylene) **53** as the macrocycle component, through which axle **55**, containing electron-rich aromatic sub-units, is threaded then stoppered to produce the [2]rotaxane **56** (Scheme 1.14).[117]



Scheme 1.14. Synthesis of rotaxane **56** *via* π-electron donor/acceptor interactions. Reagents and conditions: (i) (^{i}PrSi)$_3$OTf, lutidine, CH_3CN, RT.[117]

As well as the synthesis of rotaxanes and catenanes,[118-120] π-electron donor/acceptor templating has been used to produce a variety of different mechanically interlocked architectures, such as olympiadine, **57**, a pentacatenane, with a structure similar to the symbol of the International Olympics (Figure 1.11).[121] Other structures produced using a π-electron donor/acceptor template include daisy chains,[122] branched rotaxanes,[23, 24] rotacatenanes,[27] ring-in-ring systems[123] and figure-of-eight architectures.[124]



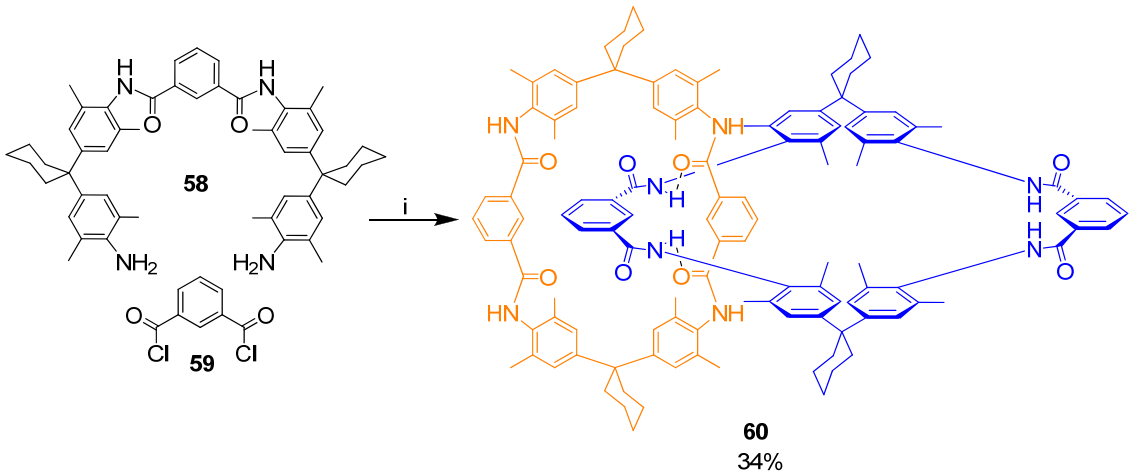
57

Figure 1.11. Structure of [5]catenane olympiadane **57**.[121]

Hydrogen Bonding

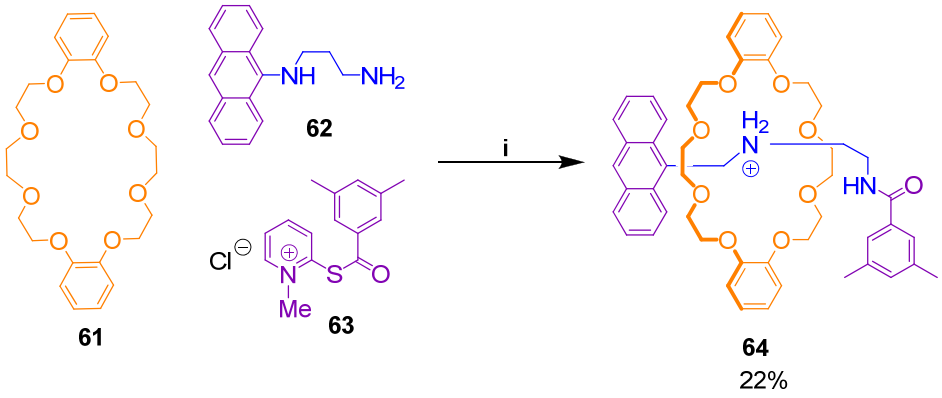
Hydrogen bonds are a wide ranging and useful form of intermolecular interaction. A variety of different functional groups can contribute to hydrogen bonding; typically amines, amides, carbonyl groups and hydroxyl groups are involved.

Hydrogen bonding as a template for the synthesis of mechanically interlocked architectures was first reported by Hunter in 1992.[125] A [2]catenane, **60**, containing intermolecular hydrogen bonds, self-assembled during an attempt to increase the yield of a previously prepared macrocycle (Scheme 1.15). The catenane was the result of the templating effect of the hydrogen bonding between two of the pre-macrocyclic threads, **58**, holding them in a position that resulted in a catenane when cyclisation was completed.



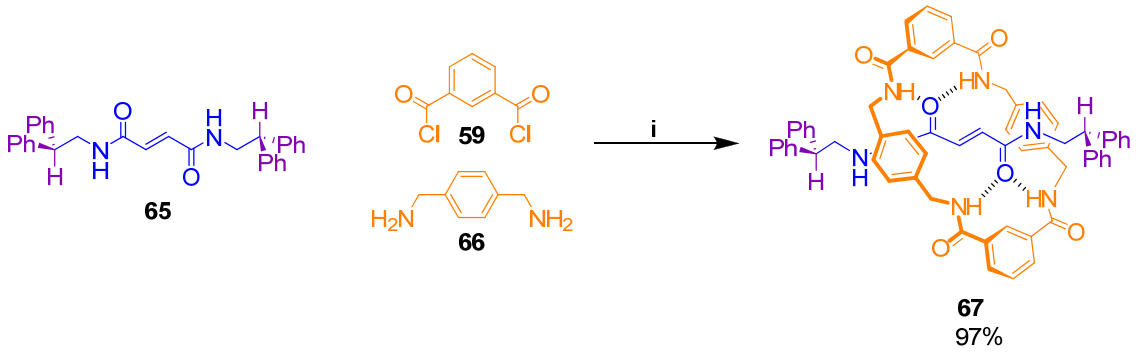
Scheme 1.15. Catenane synthesis *via* a hydrogen bond template. Reagents and conditions: (i) Et_3N, DCM, RT.[125]

As with other catenane synthesis methods, hydrogen bond templating has been developed into a methodology for the synthesis of rotaxanes.[10] A typical example of hydrogen bonding as a template in rotaxane synthesis is shown in Scheme 1.16. Axle **62**, stoppered at one end and with an amine group at the other, is threaded through crown ether **61** and held in place by hydrogen bonds between the amine and ether groups until the addition of the second stopper group, **63**, results in the formation of rotaxane **64**.[126]



Scheme 1.16. Preparation of rotaxane **64** utilising hydrogen bonding by Busch *et al.* Reagents and conditions: (i) Bu_3N, CH_3Cl_3-H_2O, RT.[126]

Development of the hydrogen bond template method by Leigh and co-workers resulted in a high yielding rotaxane synthesis through pre-organisation of the hydrogen bonding sites in the macrocycle and axle (Scheme 1.17).[127] By holding macrocycle fragments **59** and **66** around axle **65** through hydrogen bonding, and then clipping them together, Leigh *et al.* were able to attain an unprecedented 97% yield for [2]rotaxane **67**. The effectiveness of the pre-organisation allows for the use of poor hydrogen bond acceptors, even in the presence of competing acceptors, in the synthetic strategy.

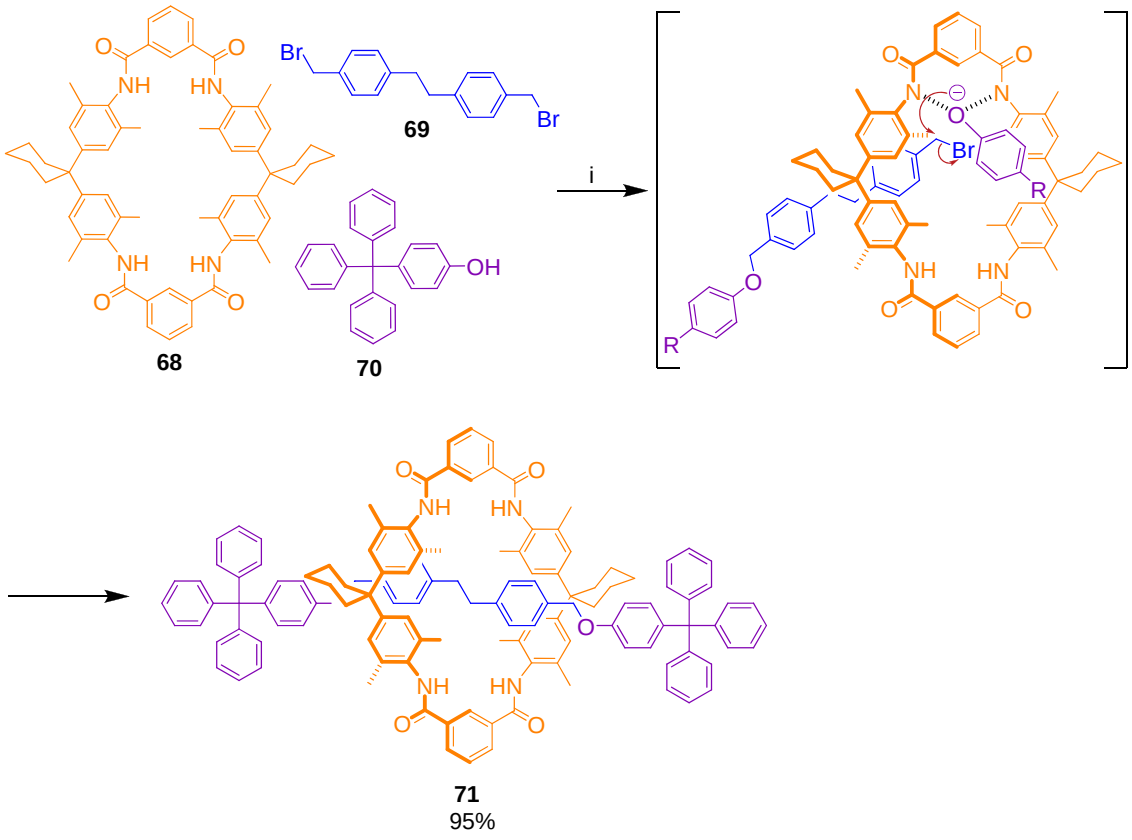


Scheme 1.17. Synthesis of rotaxane **67** *via* a hydrogen bond-mediated clipping approach. Reagents and conditions: (i) Et_3N, 1:9 CH_3CN-CH_3Cl, RT.[127]

Ionic Interactions

As well as the standard O···H and N···H hydrogen bonds, interactions between hydrogen and anionic species have also been utilised in the synthesis of rotaxanes. Vögtle and co-workers were the first to use an ionic interaction for the production of rotaxanes.[128] A pre-stoppered half-thread terminating in a phenolate ion, produced from phenol **70** *in situ*, was threaded through an amide-containing macrocycle, **68** and held in place with hydrogen-anion interactions (Scheme 1.18). Reaction of the phenolate with bromide half-thread **69** produced rotaxane **71** in an impressive 95% yield.

Vögtle has also reacted a phenolate half-thread with an acid chloride to produce a rotaxane under similar conditions.[129] Ionic interactions between hydrogen atoms and phenolate ions have also been utilised by Smith and co-workers in the formation of rotaxanes.[130, 131]

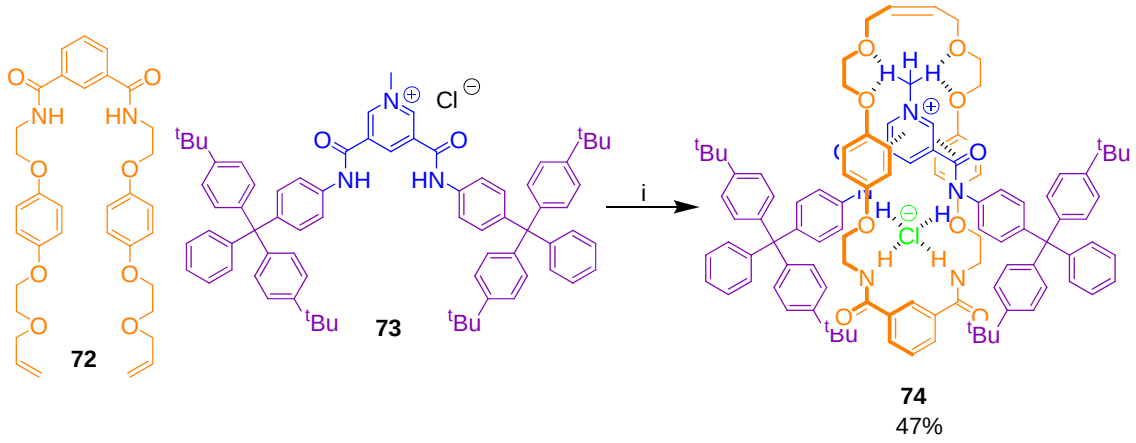


Scheme 1.18. Anion template synthesis of rotaxane **71**. Reagents and conditions: (i) K_2CO_3, DCM, RT.[128]

1.3.4. Template Synthesis – Discrete Anion Template

In addition to the use of anionic building blocks in the template synthesis of rotaxanes, discrete anions can be used to bind non-ionic components in a suitable arrangement for rotaxane formation. Beer and co-workers have pioneered the use of individual ions in the formation of mechanically interlocked structures, with halides the most common in rotaxane synthesis.[132, 133]

The first discrete anion template synthesis of a rotaxane was by Beer *et al.* in 2002.[134] A pre-macrocycle component, **72**, was held around a stoppered axle, **73**, by ion-pair interactions between the positively-charged axle and the chloride anion, and by hydrogen bonding between the anion and the amide groups (Scheme 1.19). Complementary hydrogen bonding and π-π stacking interactions at other areas between the pre-macrocycle and axle provide additional points for anchoring the components in a suitable manner for ring closing metathesis to furnish rotaxane **74** in a 47% yield.



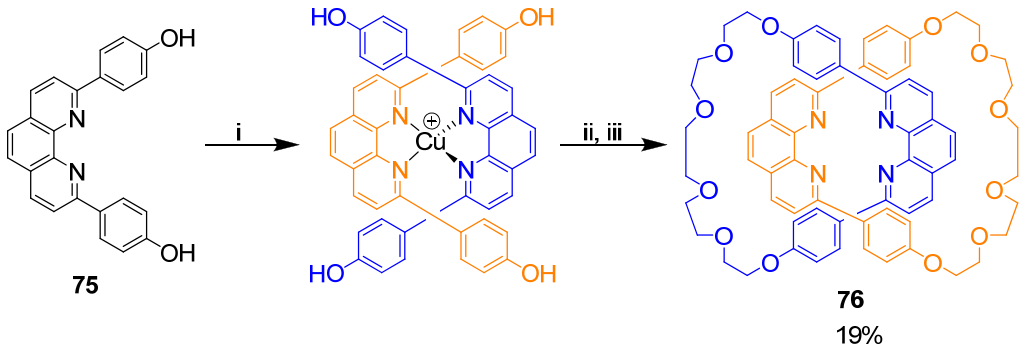
Scheme 1.19. Anion template synthesis of rotaxane **74**. Reagents and conditions: (i) Grubbs 1st generation catalyst[135] (20 mol%), DCM.[134]

This general clipping around a chloride ion template has been used in the synthesis of a daisy chain rotaxane molecule as well as for standard [2]rotaxanes.[136] Bromide has also been used in this anion template synthesis of rotaxanes.[79]

1.3.5. Template Synthesis – Passive Metal

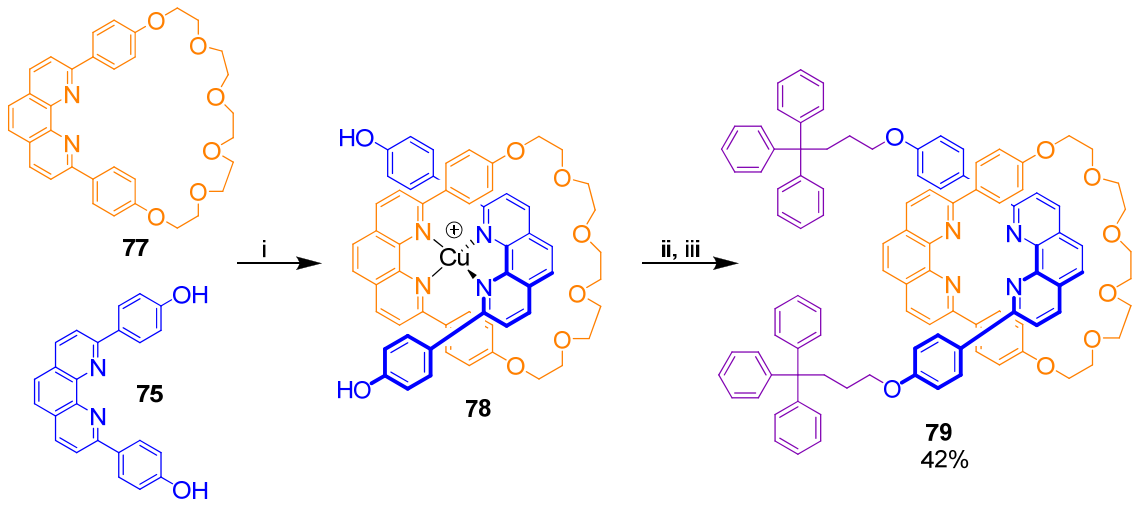
As well as anions, metals are commonly used as templates in the synthesis of rotaxanes and catenanes.[17] The rigidity of the co-ordination around the metal anchor controls the spatial orientation of the templated components in a more predictable manner than those based on intermolecular reactions between various groups on the axle and macrocycle. The choice of metals is relatively wide and offers the opportunity of different co-ordination geometries. Another advantage is the facile removal of the metal after synthesis is complete.[10]

The first metal template synthesis of an entangled structure utilised copper(I), complexing the metal with two 2,9-bus(*p*-hydroxyphenyl)-1,10-phenanthroline bidentate ligands, **75**, held in orthogonal positions to each other by the tetrahedral geometry of the copper. Cyclisation of the two ligands by addition of appropriate ring closing reagents, followed by decomplexation of the metal, resulted in the formation of the [2]catenane **76** (Scheme 1.20).[137]



Scheme 1.20. Synthesis of catenane **76** using Cu as a tetrahedral template. Reagents and conditions: (i) $[Cu(CH_3CN)_4]^+BF_4^-$; (ii) $ICH_2(CH_2OCH_2)_4CH_2I$, Cs_2CO_3, DMF; (iii) $N(CH_3)_4^+CN^-$, CH_3CN-H_2O.[137]

Metal template rotaxane synthesis also makes use of the fixed co-ordination of ligands around a metal centre.[138] One of the first rotaxane syntheses to employ metal templating uses copper(I) with phenanthroline-based macrocycle **77** and axle component **75** to form a pseudorotaxane, **78**, in a threading methodology. The pseudorotaxane is held together by the metal-ligand bonds between the copper and the two components. Stoppering of the pseudorotaxane, followed by removal of the copper, results in rotaxane **79** (Scheme 1.21).



Scheme 1.21. Cu templated synthesis of [2]rotaxane **79**. Reagents and conditions: (i) $[Cu(CH_3CN)_4]^+BF_4^-$, CH_2Cl_3-CH_3CN; (ii) $I(CH_2)_3CAr_3$, K_2CO_3, DMF-CH_3CN; (iii) amberlite-CN.[138]

Ligands are held around copper in a tetrahedral geometry. In order to access other template geometries, different metals must be used. Leigh and co-workers have pioneered the use of other metal geometries in the template synthesis of rotaxanes. These include the use of palladium for square-planar templates,[60, 139, 140] gold for linear geometries[141] and several different transition metals for the production of octahedral templates, including cobalt, manganese, nickel and zinc (Figure 1.12).[142] Takata *et al.* have also used palladium for the passive metal template synthesis of rotaxanes[143] and Sauvage and co-workers have utilised ruthenium.[144]

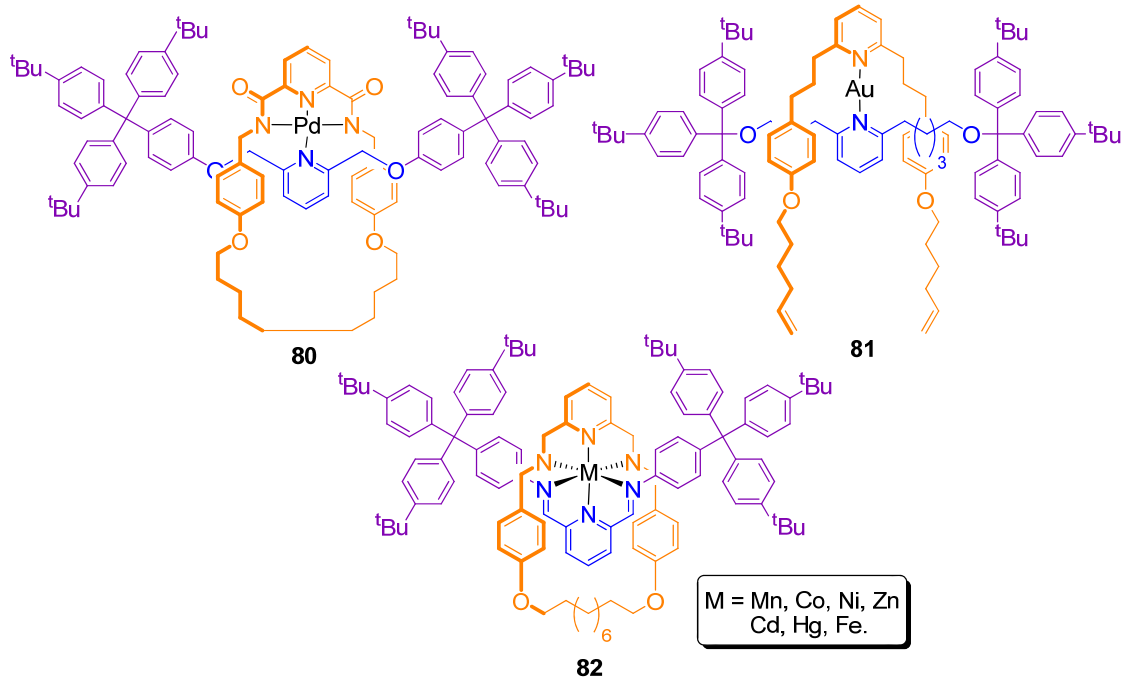
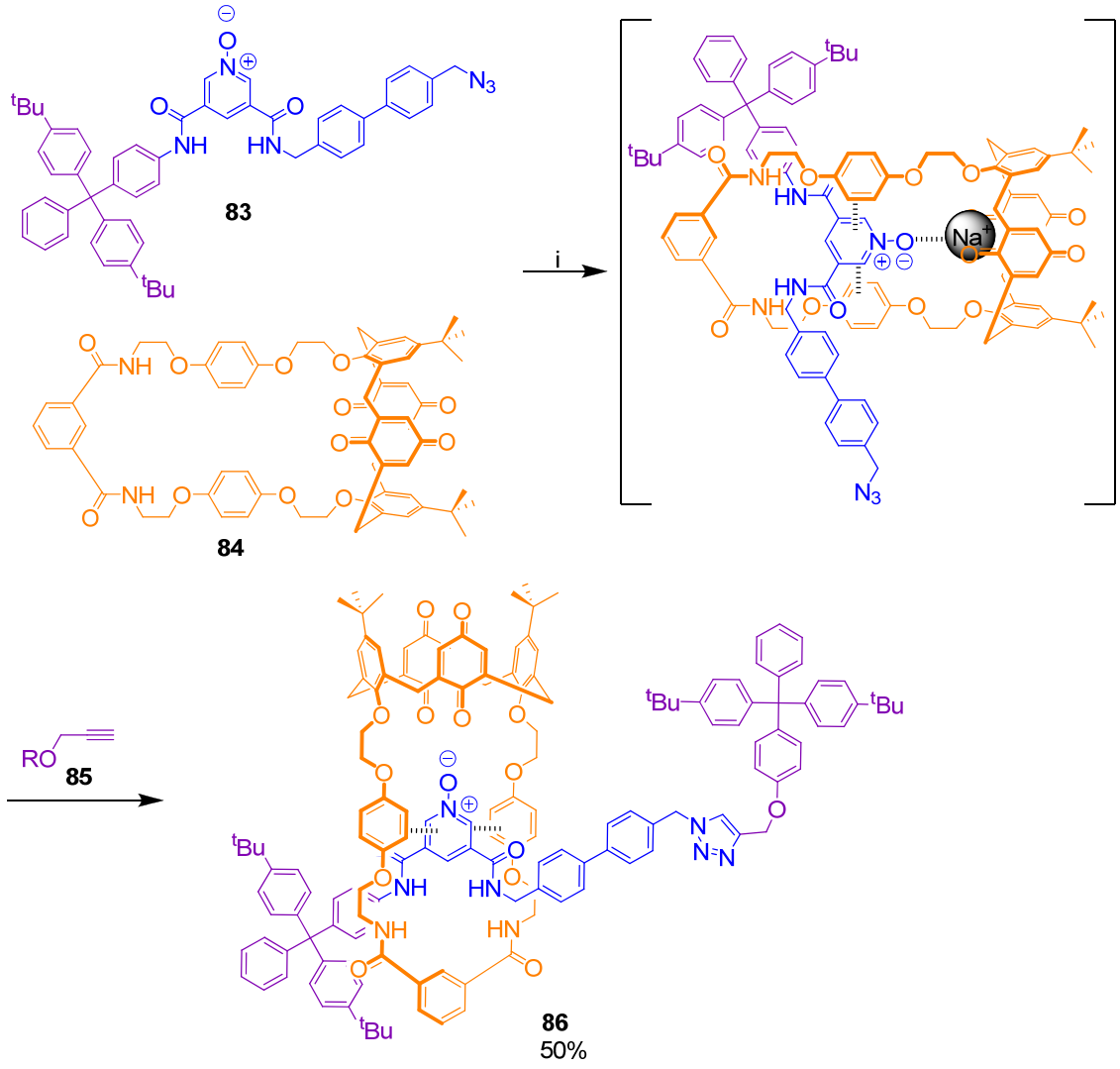


Figure 1.12. Different geometries for passive metal template synthesis of rotaxanes. Square planar with Pd (**80**);[139] linear with gold (**81**);[141] and octahedral with various metals (**82**).[142]

Transition metals are the most common metals used in this passive metal template synthesis of rotaxanes. Beer and co-workers have, however, produced rotaxanes using sodium and barium templates.[73] Macrocycle **84** contains a calix[4]diquinone group, which can bind group 1 and 2 metals. Azide half-thread **83** is threaded through macrocycle **84** and held in place with a metal-oxygen bond and complementary π-π stacking interactions (Scheme 1.22). Stoppering with alkyne **85** *via* a click reaction produces rotaxane **86** in a 50% yield when sodium is used as the templating metal.

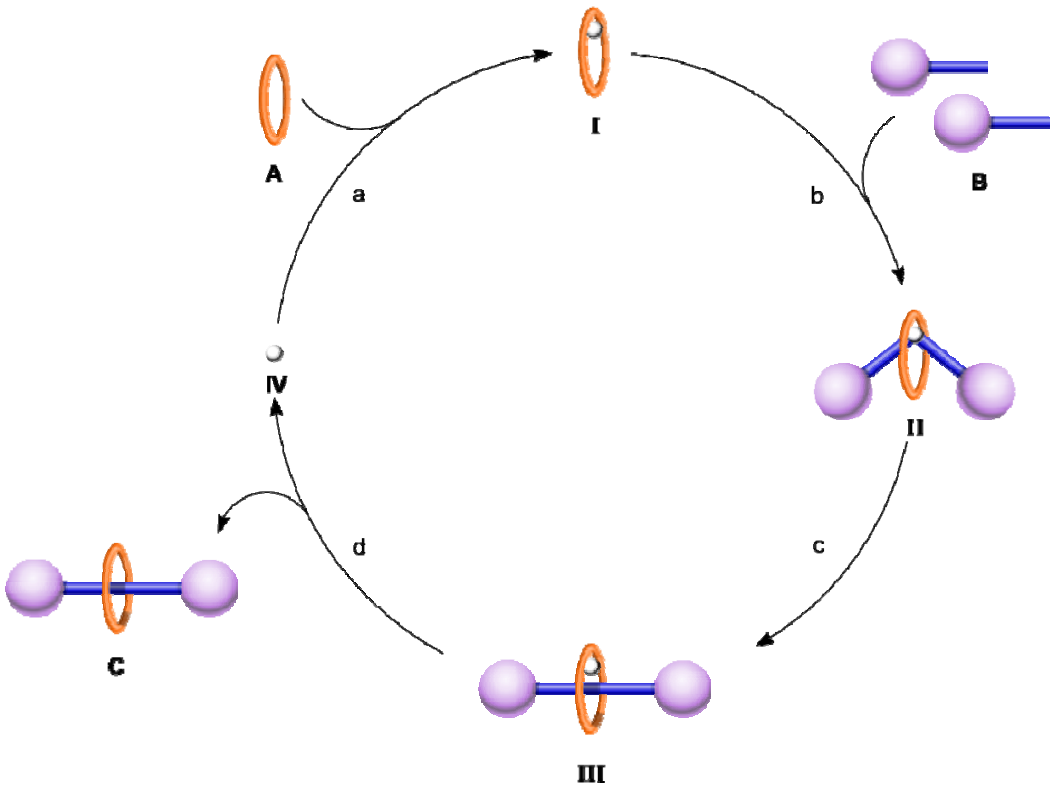


Scheme 1.22. Sodium template synthesis of rotaxane **86**. Reagents and conditions: (i) $NaClO_4$, DIPEA, $Cu(CH_3CN)_4PF_6$, DCM.[73]

1.3.6. Template Synthesis – Active Template

The use of metal templates as previously discussed can be classed as *passive* metal templating, *i.e.* the metal simply holds the two components in place whilst a covalent bond-forming reaction occurs elsewhere to provide the mechanically interlocked

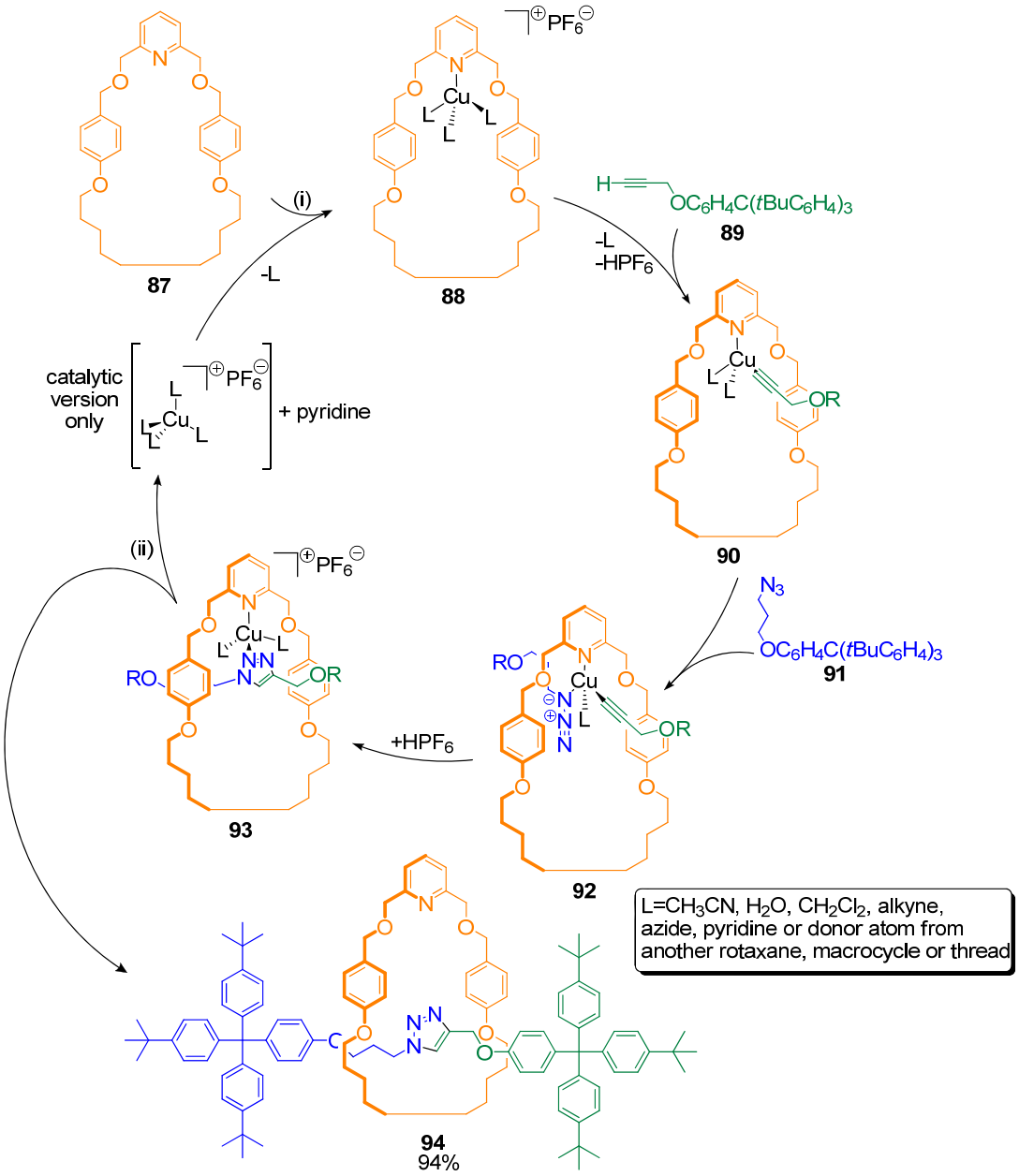
structure. However, transition metals are capable of being more than just "glue" in the synthesis of these unique architectures. There are numerous transition metal-catalysed covalent bond-forming reactions that could be utilised in the formation of entangled structures. The *active* metal template approach draws on this advantage of transition metals, incorporating metal-catalysed covalent bond-forming reactions *through* the macrocycle component in the synthesis of rotaxanes and catenanes. A foreseeable advantage of utilising these types of reactions is their catalytic nature; passive metal templates require stochiometric amounts of the metal in the reaction, but active templates can be made catalytic (Scheme 1.23). Another advantage over other templating methods is the ability to produce a rotaxane using a "traceless" synthesis, *i.e.* no permanent binding sites are required on either the axle or macrocycle.



Scheme 1.23. Catalytic active template method for formation of rotaxanes. a) Metal binds to macrocycle **A** to form species **I**. b) Two stoppered half-threads, **B**, are bound to the macrocycle-metal species **I** to produce species **II**. c) Metal-catalysed covalent bond-forming reaction to produce rotaxane **III**. d) Removal of metal to provide rotaxane product **C** and free metal **IV** to begin the cycle again.

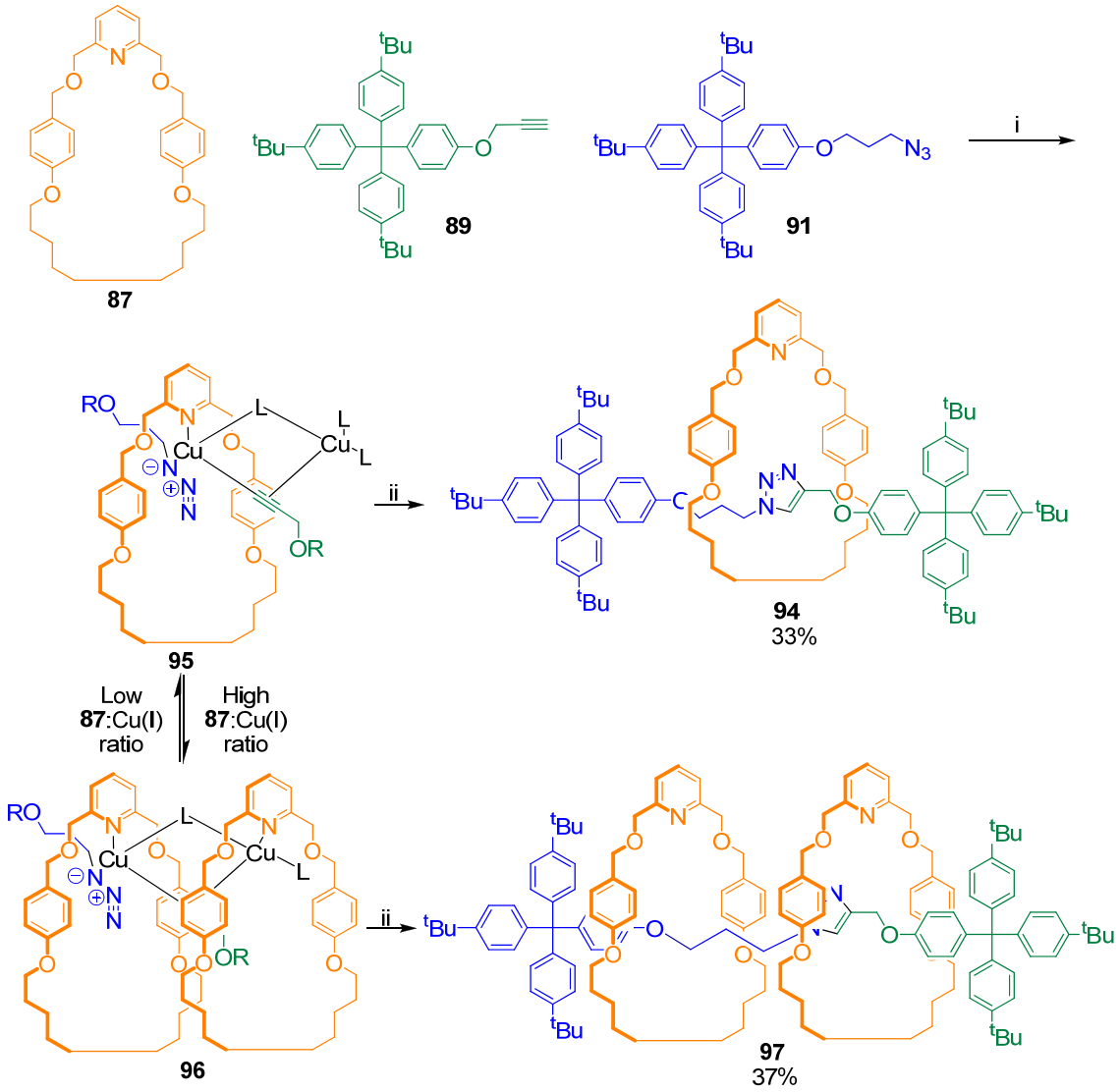
The use of transition metal-catalysed reactions to synthesise rotaxanes *via* the active template method was developed by Leigh *et al.*[145] Utilising the most common metal in traditional passive metal templating, copper, Leigh carried out a Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) 'click' reaction; a 1,3-cycloaddition of a terminal

alkyne with an organic azide (Scheme 1.24). The metal was complexed to macrocycle **87**, then stoppered alkyne half-thread **89** was added to produce complex **90**. Subsequent addition of the azide half-thread **91** resulted in complex **92**, with the two half-thread groups on opposite sides of the macrocycle. As a result, the coupling of the two half-threads *via* the copper-catalysed click reaction, followed by demetalation, formed the desired rotaxane **94** in a 94% yield. It was also determined that the reaction could be made catalytic by the addition of pyridine (Scheme 1.24); the use of substoichiometric quantities of $[Cu(CH_3CN)_4](PF_6)$ (20 mol % with respect to **87**) at 70 °C resulted in yields of rotaxane **94** of up to 82%.



Scheme 1.24. Original proposed mechanism of the CuAAC 'click' active template synthesis of rotaxane **94**. Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, DCM, RT; (ii) KCN, DCM-MeOH (plus pyridine when catalytic).[145]

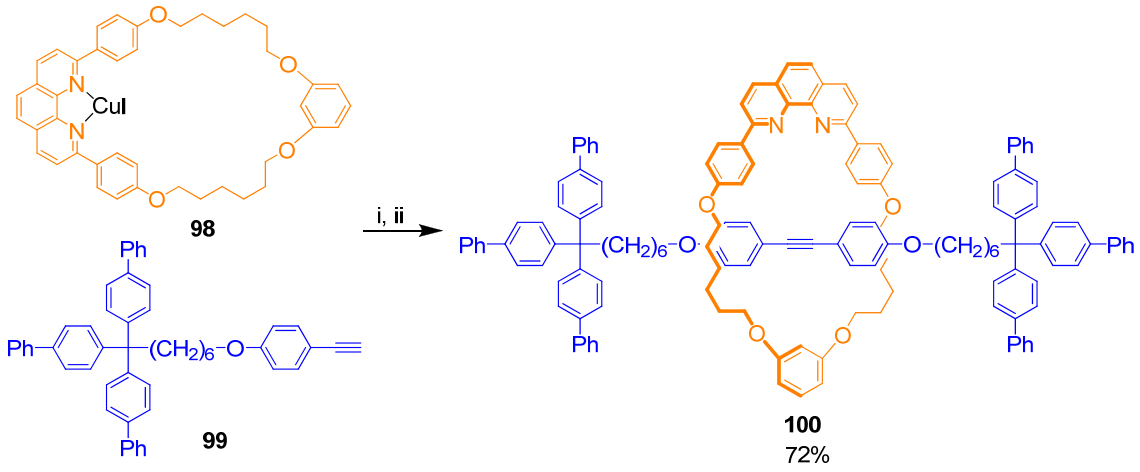
Leigh and co-workers subsequently produced a [3]rotaxane, **97**, under high macrocycle to stopper ratios using the CuAAC 'click' reaction.[43] The reaction mechanism was therefore revised to account for the formation of the [3]rotaxane (Scheme 1.25). It would appear that a second copper species is involved in the reaction, producing a bridged intermediate, **95**, which, when the ratio of macrocycle is high, binds two macrocycles, resulting in intermediate **96**, which reacts to form [3]rotaxane **97**.



Scheme 1.25. Revised mechanism for the CuAAC 'click' active template synthesis of [2]rotaxane **94** and [3]rotaxane **97**. Reagents and conditions: (i) **87** (10 eq.), $[Cu(CH_3CN)_4](PF_6)$ (1 eq.), DCM, RT; (ii) KCN, DCM-MeOH.[43]

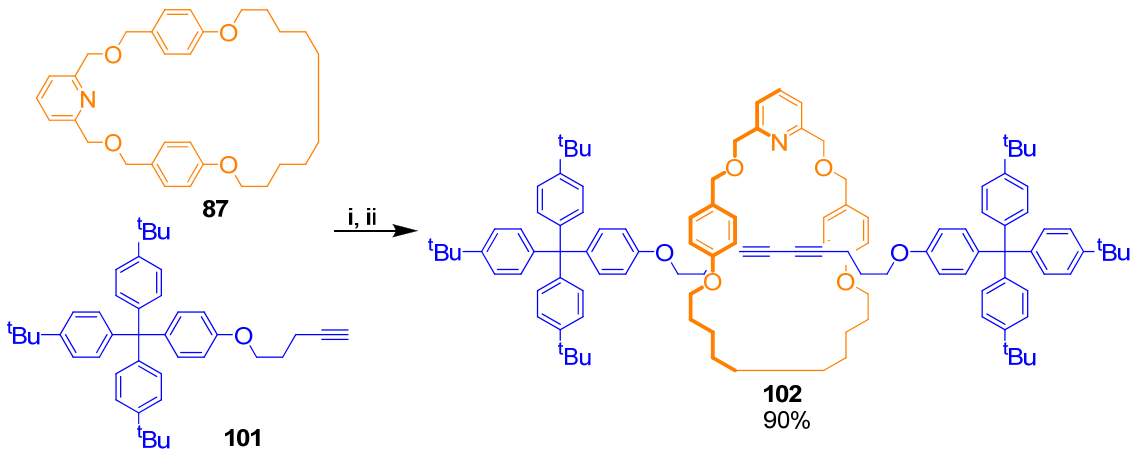
Aside from the CuAAC 'click' reaction, alkyne coupling reactions are one of the more common reactions in the active template synthesis of rotaxanes. Saito *et al.* developed the copper-mediated alkyne homocoupling formation of rotaxanes, producing rotaxane

100 in a 72% yield from copper-bound macrocycle **98** and terminal alkyne half-thread **99** (Scheme 1.26).[146] The copper-catalysed homocoupling of terminal alkynes has also been utilised by Anderson and Gladysz in the formation of rotaxanes; some with a polyyne thread[147, 148] and one with porphyrin stopper groups.[149]



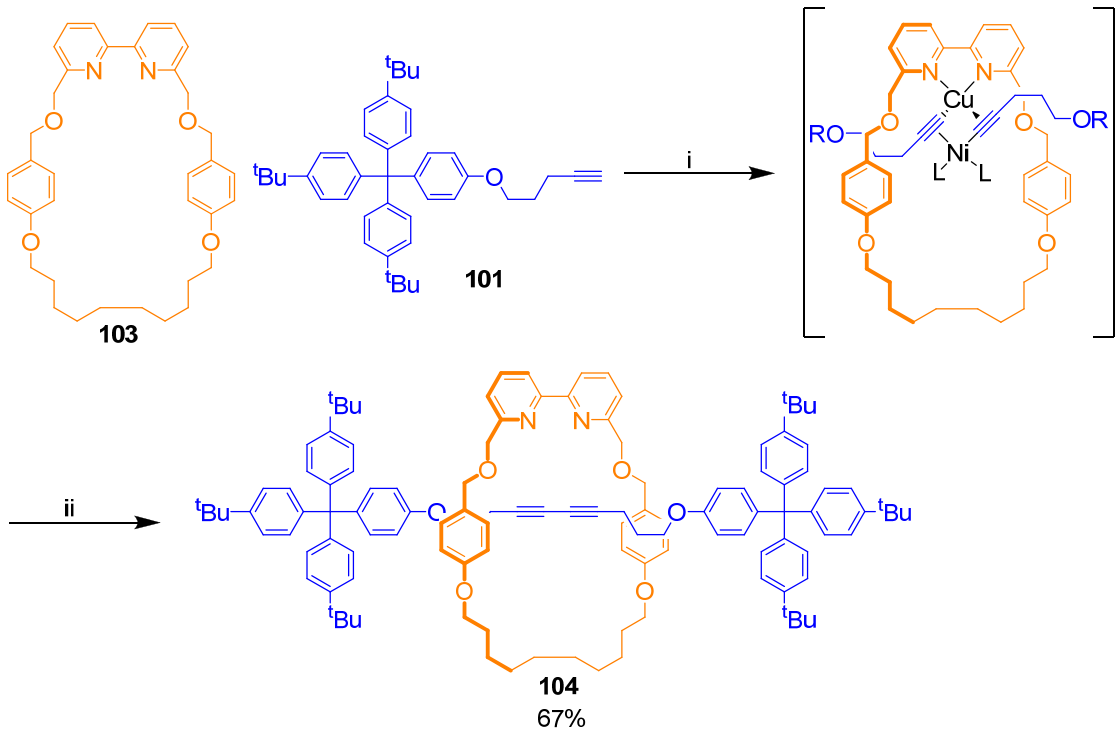
Scheme 1.26. Copper-catalysed alkyne homocoupling active template synthesis of rotaxane **100**. Reagents and conditions: (i) K_2CO_3, I_2, toluene, 110 °C; (ii) KCN, DCM-CH_3CN.[146]

Leigh has developed the use of other metals in the active template alkyne homocoupling synthesis of rotaxanes. The palladium(II)-catalysed synthesis of rotaxane **102** from macrocycle **87** and alkyne half-thread **101** achieved an impressive 90% yield (Scheme 1.27).[150]



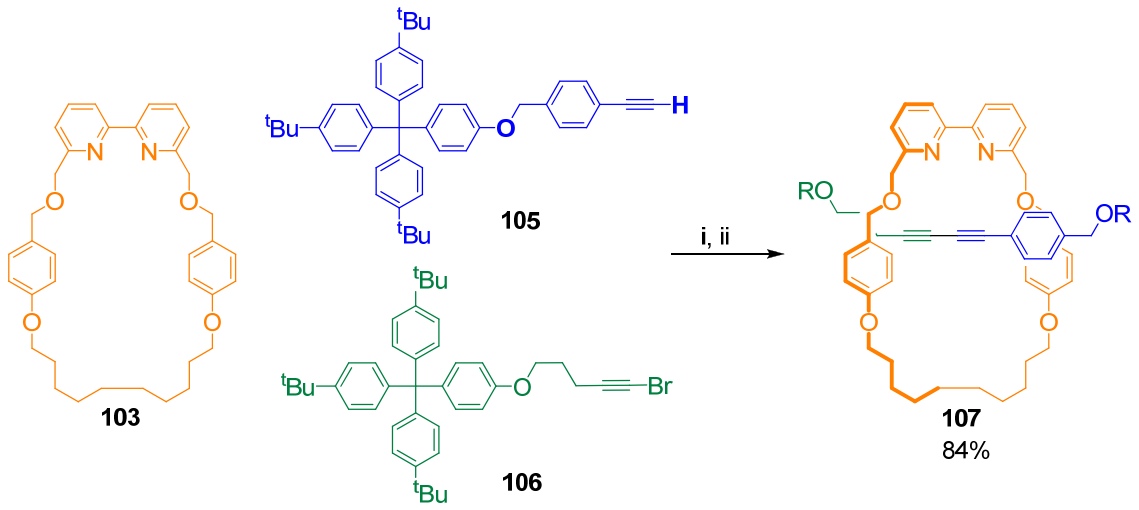
Scheme 1.27. Palladium-catalysed alkyne homocoupling active template synthesis of rotaxane **102**. Reagents and conditions: (i) DIPA, CuI, I_2, **87**·Pd[CH_3CNCl_2], benzene; (ii) Na_4EDTA, DCM.[150]

A novel nickel/copper bimetallic system, where both metals are involved in the catalytic step, forming a 5-membered bimetallic system with macrocycle **103** and two molecules of half-thread **101**, produced rotaxane **104** in a 67% yield (Scheme 1.28).[151]



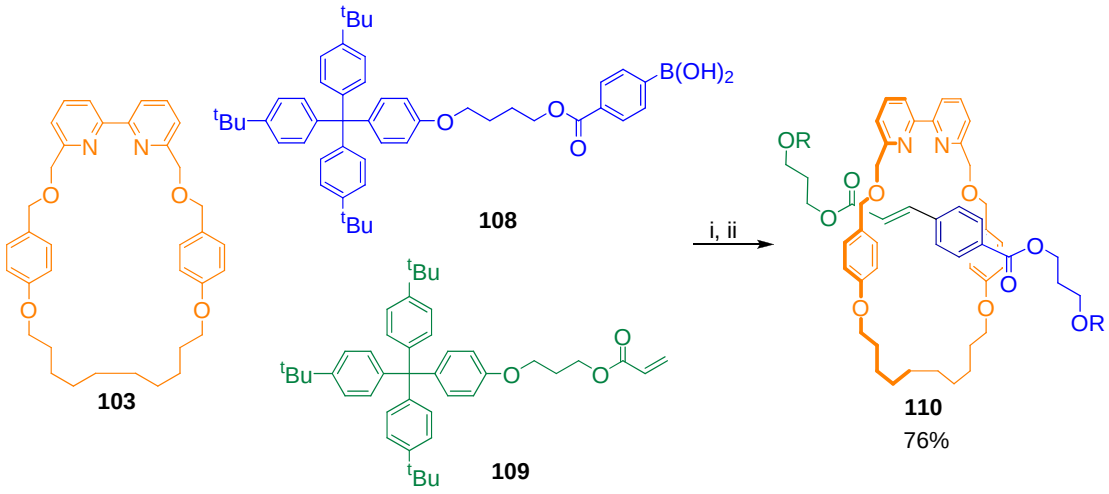
Scheme 1.28. Nickel/copper bimetallic-catalysed alkyne homocoupling active template synthesis of rotaxane **104**. Reagents and conditions: (i) **103**·$NiCl_2$, *n*-BuLi, CuI, THF, -70 °C → 80 °C; (ii) Sat. EDTA in 17.5% aq. NH_3, DCM.[151]

The copper-catalysed Cadiot-Chodkiewicz heterocoupling of terminal alkynes was used by Leigh and co-workers to produce a non-symmetric dialkyne threaded rotaxane **107**. **107** was achieved in an 84% yield from macrocycle **103**, terminal alkyne half-thread **105** and bromide half-thread **106** (Scheme 3.5).[152]



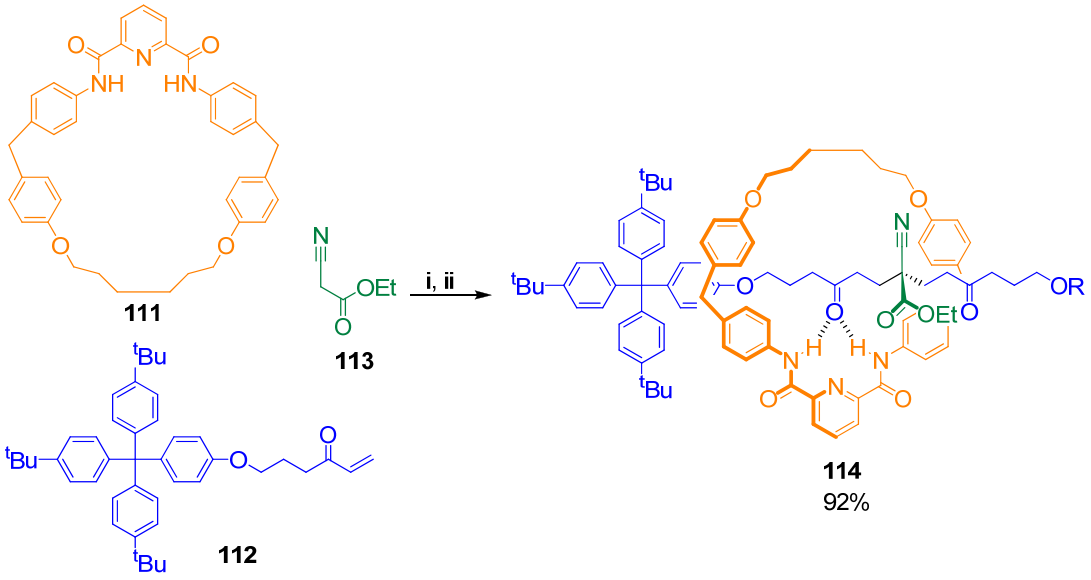
Scheme 1.29. Cadiot-Chodkiewicz active template synthesis of rotaxane **107**. Reagents and conditions: (i) *n*-BuLi, CuI, THF, -78 °C → RT; (ii) Sat. EDTA in 17.5% aq. NH_3.[152]

As well as the CuAAC 'click' and alkyne coupling reactions, other well-known reactions have been developed for the active template synthesis of rotaxanes. Leigh *et al.* have developed the palladium(II)-catalysed oxidative Heck cross-coupling reaction for the synthesis of rotaxanes.[153] The reaction couples boronic acid **108** with alkene **109** on the Pd(II) complex of macrocycle **103**, producing unsymmetrical rotaxane **110** in a 76% yield (Scheme 3.12).



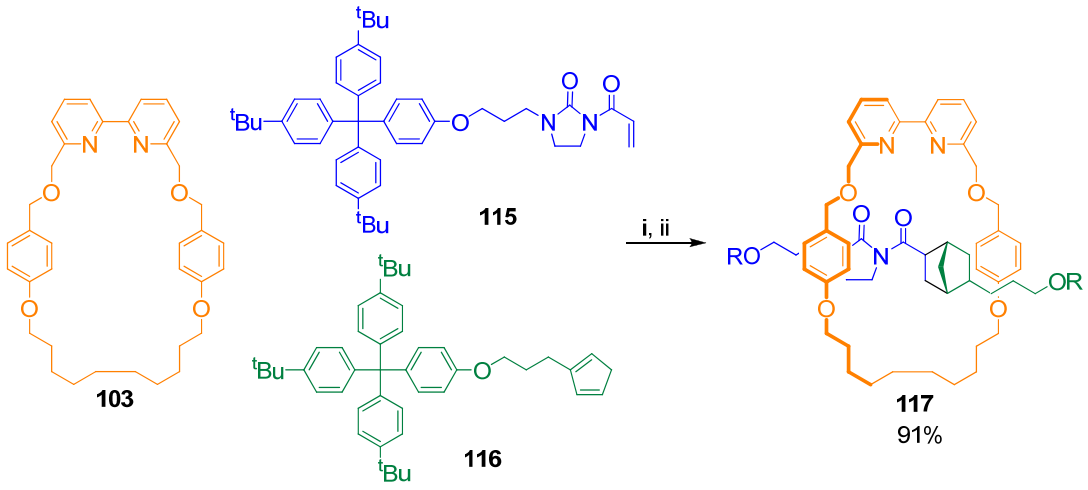
Scheme 1.30. Oxidative Heck active metal synthesis of rotaxane **110**. Reagents and conditions: (i) $Pd(OAc)_2$, benzoquinone, $CHCl_3$-DCM, O_2, RT; (ii) KCN, MeOH, $CHCl_3$-DCM.[153]

Palladium is also used to produce rotaxanes *via* Michael additions of vinyl ketones to ethyl cyanoacetate, **113**.[154] **113** is bound to the palladium(II) complex of macrocycle **111** and undergoes the palladium-catalysed double addition of vinyl ketone stopper **112**. Removal of the palladium provides rotaxane **114** in a 92% yield (Scheme 1.31).



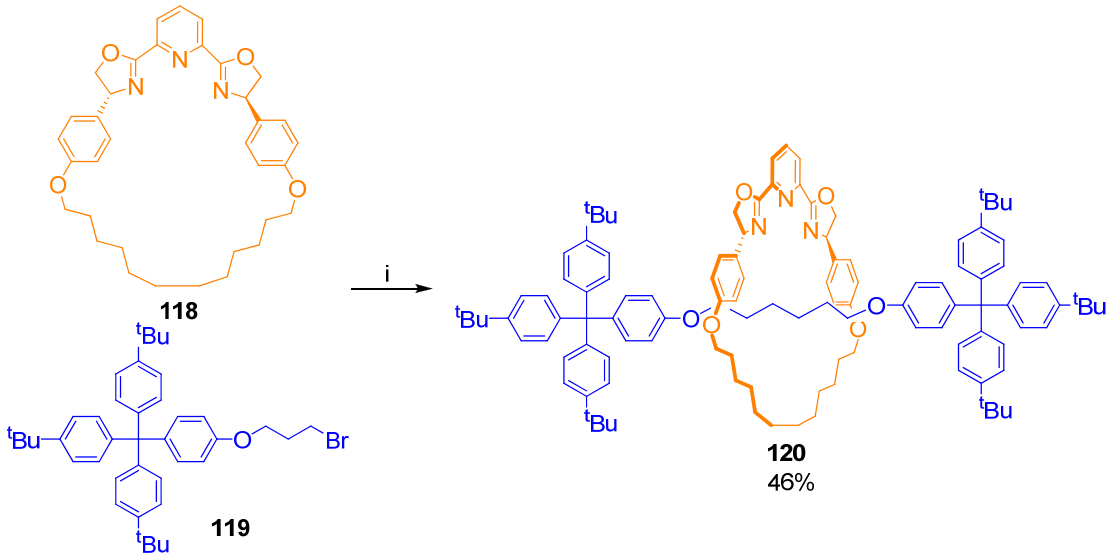
Scheme 1.31. Palladium-catalysed Michael addition active template synthesis of rotaxane **114**. Reagents and conditions: (i) [**111**Pd(CH_3CN)], DIPEA, DCM, 40 °C; (ii) HCl (1M), DCM, reflux.[154]

The copper-catalysed Diels-Alder reaction has also been developed for active template synthesis of rotaxanes.[59] Binding of the dieneophile, acryloyl imidazolidone half-thread **115**, with the Lewis acid copper species of macrocycle **103**, activates it for reaction with the diene, **116**. Cycloaddition between **115** and **116**, followed by demetallation, furnishes rotaxane **117** in a 91% yield (Scheme 1.32).



Scheme 1.32. Copper-catalysed Diels-Alder active template synthesis of rotaxane **117**. Reagents and conditions: (i) $Cu(OTf)_2$, DCM, -78 °C → RT; (ii) NH_3 (35% aq.).[59]

Leigh and co-workers discovered a new nickel-catalysed sp^3-sp^3 homocoupling of unactivated alkyl bromides and developed it for the active template synthesis of rotaxanes.[155, 156] Two molecules of bromide half-thread **119** bind to the nickel complex of macrocycle **118** *via* oxidative addition. Reductive elimination and demetallation then result in rotaxane **120** in a 46% yield (Scheme 1.33).



Scheme 1.33. Nickel-catalysed sp^3-sp^3 homocoupling active template synthesis of rotaxane **120**. Reagents and conditions: (i) $NiCl_2$·DME, Zn, NMP, THF, RT. [155]

1.4. Mechanical Planar Chirality

Topological chirality, chirality which occurs due to the interconnected structure of a species rather than any chirality present within its individual components, is a feature of mechanically interlocked species.[1] Prime knots, such as the trefoil knot, are inherently chiral structures, with non-superimposable mirror images created by the interweaving of a single component.[1] Catenanes, on the other hand, are not inherently chiral; they consist of two or more components and if either of those components is symmetrical, *i.e.* have no directionality, then the structure will be topologically achiral.[157] However, if both components are asymmetric, a topologically chiral species is produced.[157]

Rotaxanes, as discussed in Section 1.1, page 2, are not technically topological structures as, in theory, they could be decomposed to their constituent parts without breaking bonds. However, as in reality this is not possible, rotaxanes can be considered to possess chirality based on their interlocked structures if both components, macrocycle and axle, are asymmetric. Mechanical planar chirality in rotaxanes (sometimes referred to as 'cyclochirality')[158] arises from the threading of an asymmetric macrocycle, *i.e.* one that possess directionality in its structure, with an asymmetric axle. The two enantiomers thus formed differ by the orientation of the macrocycle with respect to the axle (Figure 1.13).[158]

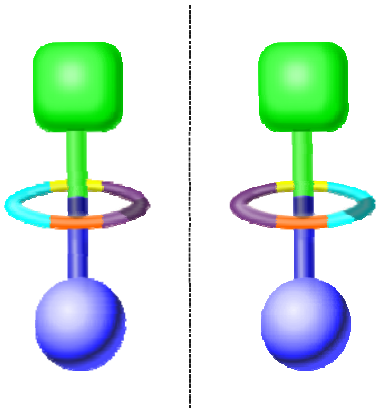


Figure 1.13. Mechanical planar chirality in rotaxanes.

Preparation of enantiopure mechanically planar chiral rotaxanes, *i.e.* those possessing only planar chirality in their structures, is a relatively unexplored topic in the field of mechanically interlocked structures.[157] There are two main approaches to the synthesis of a planar chiral enantiomer; preparation of a racemic mixture followed by resolution or the asymmetric preparation of one enantiomer, although the latter has been less successful.

1.4.1. Racemic Synthesis

Vögtle *et al.* produced the first example of a racemic mixture of planar chiral rotaxane enantiomers, **121** and **122**, containing no other forms of chirality (Figure 1.14). This mixture was then found to undergo enantioseparation *via* preparative chiral HPLC.[159]

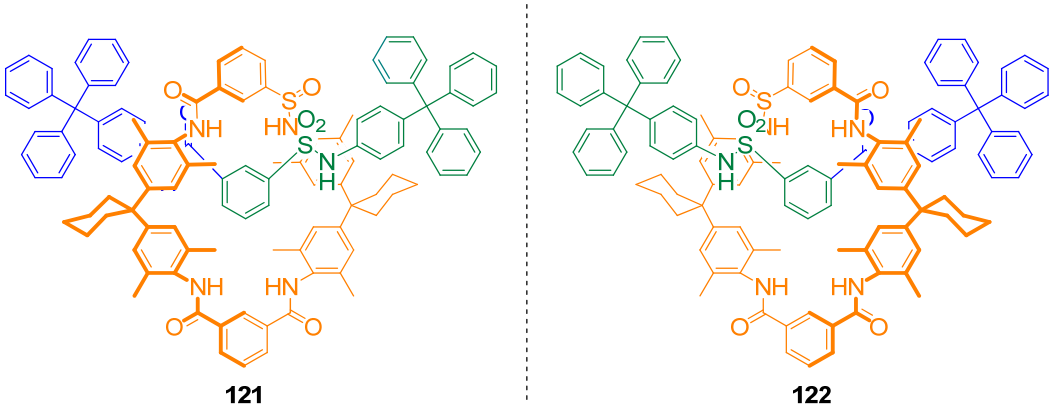


Figure 1.14. Racemic mixture of mechanically planar chiral rotaxanes **121** and **122**.[159]

Hiratani and co-workers were also successful in preparing racemic rotaxane mixtures which were then resolved using preparative chiral HPLC (Figure 1.15).[84, 99] However, not all of the racemates proved receptive to enantioseparation by chiral HPLC, illustrating that not all planar chiral rotaxanes can be purified in this manner.[99]

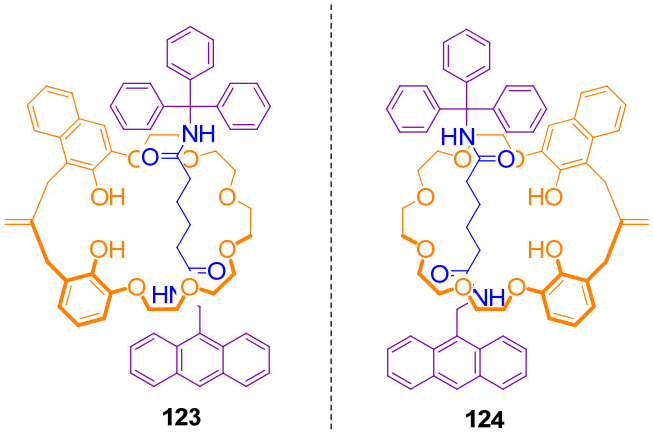
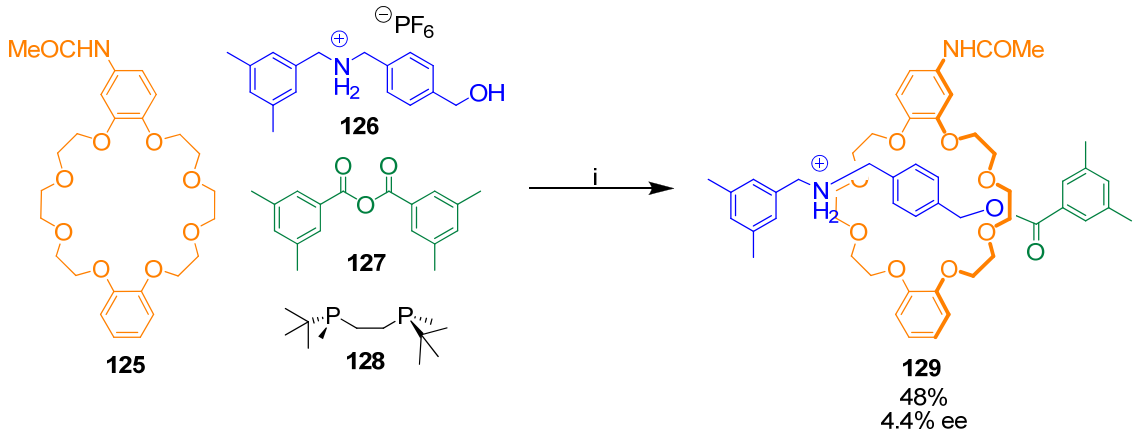


Figure 1.15. Racemic mixture of mechanically planar chiral rotaxanes **123** and **124**.[99]

1.4.2. Asymmetric Synthesis

As well as the inability to separate all racemic mixtures produced, the racemic synthesis method for the production of enantiopure planar chiral rotaxanes also suffers from yield limitations, with the largest yield possible for one enantiomer being 50%. Asymmetric synthesis, where only one of the possible enantiomers is selectively formed, would address these issues. However, there are challenges inherent in this method of synthesis

and to date only one attempt has been reported.[160] Takata and co-workers used chiral trialkylphosphane **128** as a catalyst which interacted with unsymmetrical macrocycle **125**, secondary amine salt **126** and 3,5-dimethylbenzoic anhydride **127**, resulting in the asymmetric synthesis of the planar chiral rotaxane **129** in a 48% yield (Scheme 1.34). However, the rotaxane was only produced in a 4.4 % ee, illustrating how difficult asymmetric synthesis of this type of system is.



Scheme 1.34. Asymmetric synthesis of rotaxane **129**. Reagents and conditions: (i) Et_3N, $CHCl_3$, RT.[160]

Lacour *et al.* attempted the diastereoselective synthesis of an inherently chiral pseudorotaxane, with a chiral stopper group. The stopper group is used as a chiral auxiliary to direct the approach of an unsymmetrical macrocycle onto the thread component. However, a mixture of two diastereomers, **130** and **131**, was produced, with a de of < 8% (Figure 1.16).

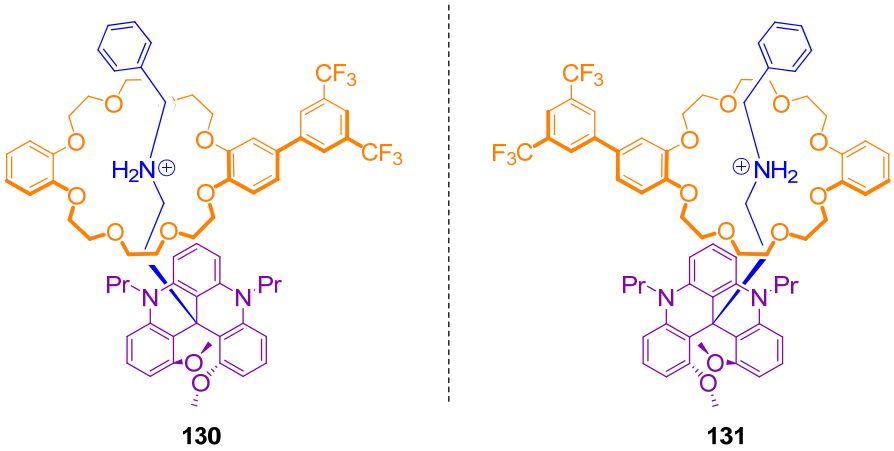
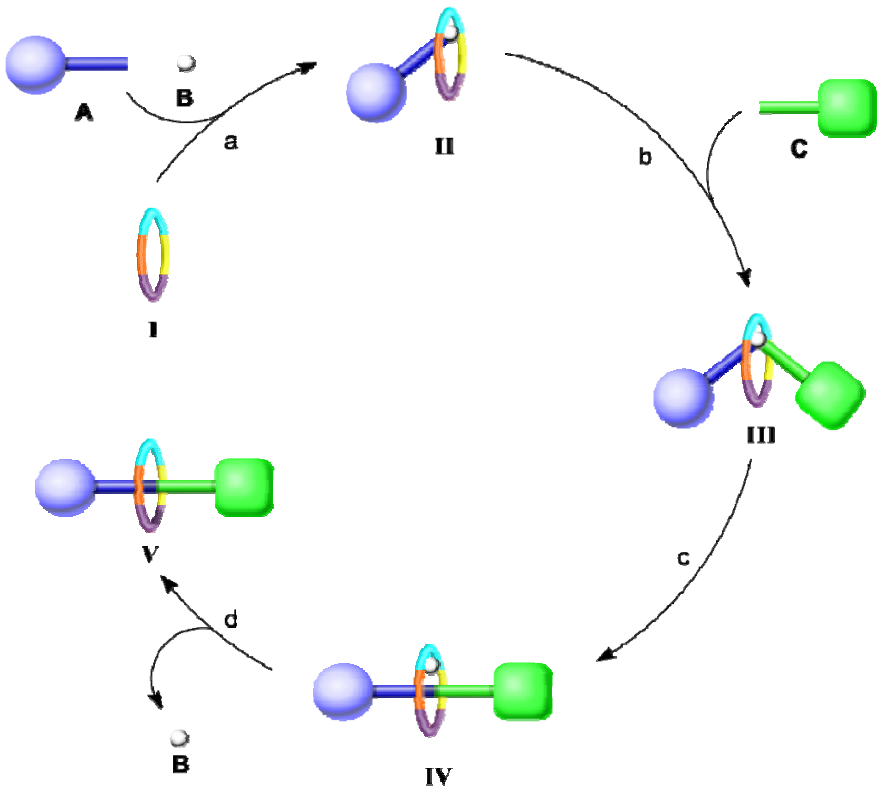


Figure 1.16. Diastereomeric rotaxanes **130** and **131**.[157]

1.5. Research Outline

The aim of this project is the asymmetric synthesis of an enantiopure mechanically planar chiral rotaxane, containing no other forms of chirality. To achieve this, an *asymmetric active template method* will be developed (Scheme 1.35). This approach uses a *hetero*coupling reaction to bring together two distinct stoppered half-threads through the macrocycle. The macrocycle will be completely asymmetric and produce a metal-macrocycle complex with two sterically different faces, *e.g.* by the presence of point chirality in the macrocycle. Approach of the first half-thread will be to the *least* hindered face of the macrocycle, with the second having no choice, due to the co-ordination demands of the metal centre, but to attack opposite the first half-thread, *i.e.* to the *more* sterically hindered face of the macrocycle. Formation of the covalent bond *via* the metal-catalysed heterocoupling reaction followed by demetalation should result in only one diastereomer. Subsequent removal of the point chirality present in the macrocycle would furnish an enantiopure mechanically planar chiral rotaxane.



Scheme 1.35. Proposed asymmetric active template for rotaxane formation. a) Approach of first half-thread **A** and metal **B** to less sterically hindered face of asymmetric macrocycle **I**. b) Approach of second half-thread **C** to species **II** to give species **III**. c) Covalent bond-forming reaction to form rotaxane **IV**. d) Removal of metal to furnish planar chiral rotaxane **V**.

Chapter 2

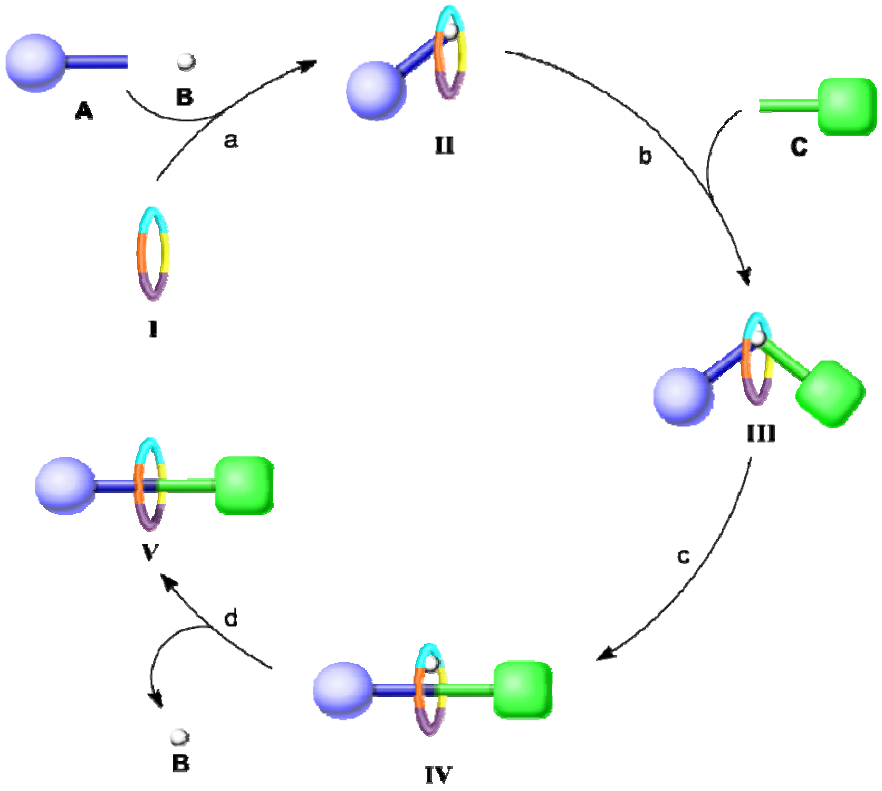
Synthesis of Macrocycle

Chapter 2: Synthesis of Macrocycle

2.1. Introduction

2.1.1. Macrocycle Design

The basis of the proposed asymmetric synthesis of mechanically planar chiral rotaxanes discussed in Chapter 1 (Scheme 2.1) is the production of a suitable macrocycle component. The macrocycle should lack any element of symmetry and produce a metal-macrocycle complex with sterically different faces. In the final rotaxane, the macrocycle must not possess any form of chirality to produce an enantiopure rotaxane. As well as this, the macrocycle must be able to bind to a metal centre and be a ligand in a metal-catalysed covalent bond-forming reaction, which should occur within its cavity. It should then be able to easily dissociate from the metal in order to yield a rotaxane. Ideally, the macrocycle should be able to act as a ligand in various different metal-catalysed reactions to provide a large scope for possible rotaxane-forming reactions.



Scheme 2.1. Proposed asymmetric active template for rotaxane formation. a) Approach of first half-thread **A** and metal **B** to less sterically hindered face of asymmetric macrocycle **I**. b) Approach of second half-thread **C** to species **II** to give species **III**. c) Covalent bond-forming reaction to form rotaxane **IV**. d) Removal of metal to furnish planar chiral rotaxane **V**.

The vast majority of active template syntheses of rotaxanes employ pyridine- or bipyridine-based, planar, symmetrical macrocycles which are unsuitable for the proposed asymmetric synthesis of rotaxanes due to the requirement for an unsymmetrical, non-planar macrocycle.[17, 161] Although chiral bipyridine molecules are known, including a chiral macrocycle,[162] and have been used as ligands in a variety of metal-catalysed asymmetric reactions,[163] the point chirality present is difficult to remove once it is no longer required. With this in mind, it was decided to move away from pyridine-based macrocycles and look at different functional groups. Groups possessing point chirality which could be easily removed at a later stage, *i.e.* after the synthesis of the rotaxane, were of interest. To this end the possibility of a bis(oxazoline) (Box) macrocycle for the asymmetric synthesis of rotaxanes was investigated as the point chirality in these molecules can be removed by oxidation under mild conditions (*vide infra*).

2.1.2. Bis(oxazoline)s

Bis(oxazoline)s are, as the name suggests, compounds which contain two oxazoline rings. Oxazolines are five-membered rings which possess a nitrogen atom, an oxygen atom and a double bond. There are three possible forms of oxazoline; 2-oxazolines, 3-oxazolines and 4-oxazolines (Figure 2.1), with 2-oxazolines by far the most common.[164, 165] They were first produced by Andreasch in 1884[164] and have many applications, including their most prominent usage to date, in asymmetric catalysis.[165-167]

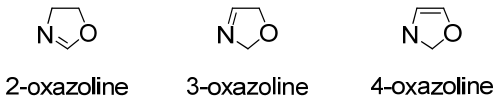


Figure 2.1. Possible structures of oxazolines.

There is a wide variety of structures available in the bis(oxazoline) family, giving this class of compounds diversity in their physical and chemical properties. The most basic bis(oxazoline) structure is that where the two oxazoline rings are directly connected to each other (**A**, Figure 2.2).[166, 168] The most commonly utilised bidentate bis(oxazoline) ligands are those with a one-carbon spacer between the oxazoline rings (**B**, Figure 2.2). There is a large variety of structures based on this simple Box ligand due to the ability to incorporate a wide range of groups onto the spacer carbon atom (R' in **B**, Figure 2.2).[166, 168, 169] Examples include alkyl chains, aromatic groups and carbocycles such as

cyclopropane and cyclobutane. Another group of bidentate Box ligands with a one-atom spacer are the aza-bis(oxazoline)s (azabox), where the spacer is a tertiary nitrogen atom (**C**, Figure 2.2). Bidentate Box ligands with two atoms between the oxazole rings are also available, although not as numerous as the malonate-based structures (**D**, Figure 2.2).[166, 168] Again, various structures can be achieved by substitution on the backbone of the molecule.

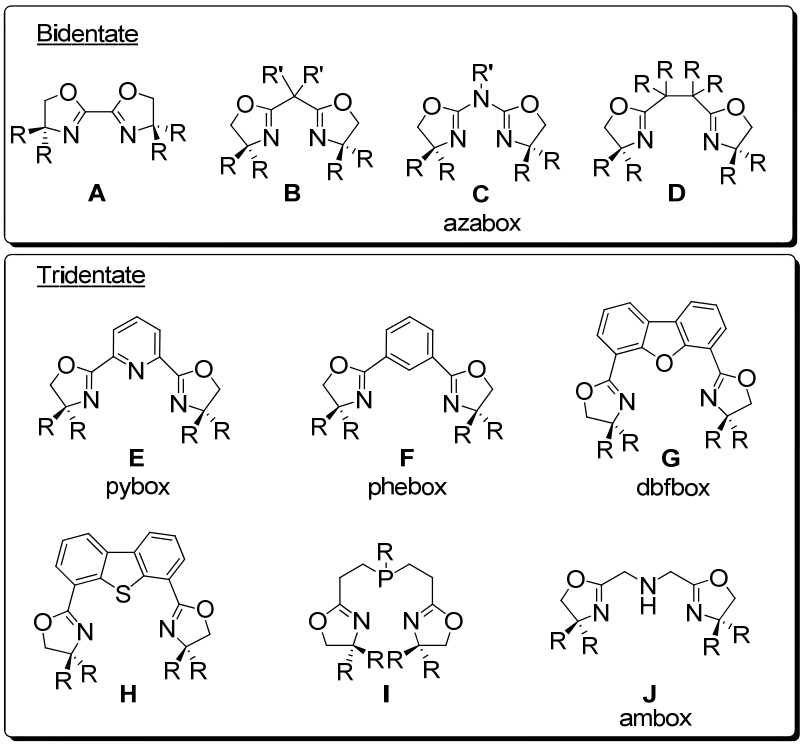


Figure 2.2. Bis(oxazoline) structures.

Tridentate bis(oxazoline) compounds are also common, with pyridine-bis(oxazoline) (pybox) ligands of most interest (**E**, Figure 2.2).[166-168] Other examples include phenol-Box (phebox, **F**, Figure 2.2), dibenzofurandiyl-Box (dbfbox, **G**, Figure 2.2), dibenzothiophene-Box (**H**, Figure 2.2), phosphine-Box (**I**, Figure 2.2) and amine-Box (ambox, **J**, Figure 2.2).

2.1.3. Symmetry in Bis(oxazoline)s

The vast majority of bis(oxazoline)s in the literature are symmetrical molecules, with C_2-symmetry (Figure 2.3). There are very few examples in the literature of asymmetric malonate-type bis(oxazoline)s with dissymmetry in the pendant groups. There are, however, numerous examples of asymmetric Box compounds with the dissymmetry present in the backbone.[170-185] C_1-symmetric bis(oxazoline)s with different pendant groups on opposite faces of the molecule, similar to their C_2-symmetric counterparts

(C_1-I, Figure 2.3) are reported by several groups. García *et al.* synthesised a range of asymmetric ligands utilizing a zinc-mediated coupling of a cyanide-containing oxazole and an amino alcohol.[186] The more standard synthesis of one-carbon spacer bis(oxazoline) ligands, from a disubstituted malonic acid derivative and amino alcohols,[169] was followed by Benaglia *et al.* in their synthesis of a C_1-symmetric Box ligand with a chelating side arm for stereoselective Mukaiyama aldol condensations.[187]

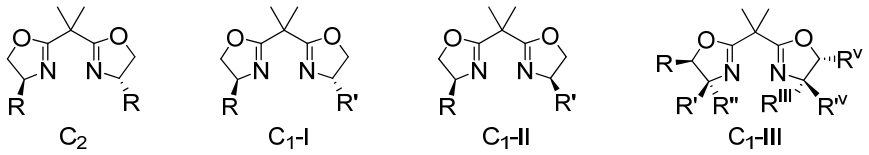
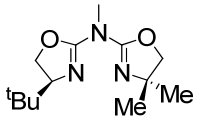


Figure 2.3. Symmetry in bis(oxazoline)s.

There are even fewer reports of C_1-symmetric bis(oxazoline)s with both pendant groups on the same face of the molecule (C_1-II, Figure 2.3). García *et al.* synthesised a C_1-symmetric azabox molecule, **132**, where two different pendant groups were in the same plane of the molecule, although there was also a pendant group on the other face (Figure 2.4).[188] The García group have also produced C_1-symmetric bis(oxazoline)s based on different pendant groups at various points around the Box moiety (C_1-III, Figure 2.3).[189] We do not believe that any examples of a C_1-symmetric bis(oxazoline) of type II with no additional pendant groups are present in the literature. It is this type of structure which would provide the basis for the steric differentiation in the faces of the macrocycle required for the asymmetric synthesis of planar chiral rotaxanes.



132

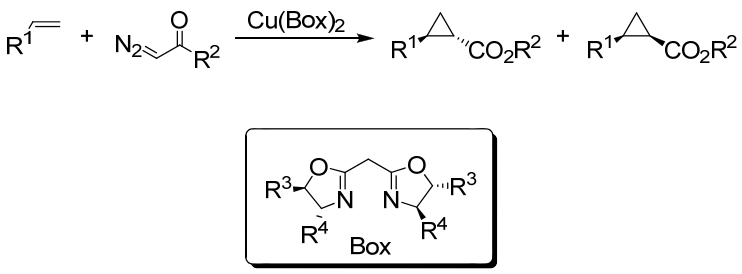
Figure 2.4. C_1-symmetric aza-bis(oxazoline) **132**.[188]

2.1.4. Bis(oxazoline)s in Catalysis

Bis(oxazoline)s are one of the most popular classes of ligands in asymmetric catalysis.[166-169, 190, 191] They are known to bind to a wide range of different metals such as copper, zinc, magnesium, nickel, palladium, *etc* and are used as ligands in a wide range of reactions. Evans[192] and Corey[193] kick-started the use of bis(oxazoline)s in asymmetric catalysis with back-to-back publications in the *Journal of the American Chemical Society* in 1991 on the use of Box ligands in cyclopropanation and Diels-

Alder reactions respectively. Since then, the use of bis(oxazoline) ligands in asymmetric catalysis has rapidly expanded.

Cyclopropanation reactions are one of the most popular reactions in which bis(oxazoline) ligands are used as chiral catalysts.[190] Masamune *et al.* were the first to use Box ligands in the cyclopropanation of olefins, reporting a range of starting materials (Scheme 2.2).[194] Interest in bis(oxazoline)s as more accessible alternatives to the chiral semicorrins developed by Pfaltz[195] for cyclopropanation reactions was widespread, with new chiral bis(oxazoline) ligands for cyclopropanations still a topic for research.[196-198]



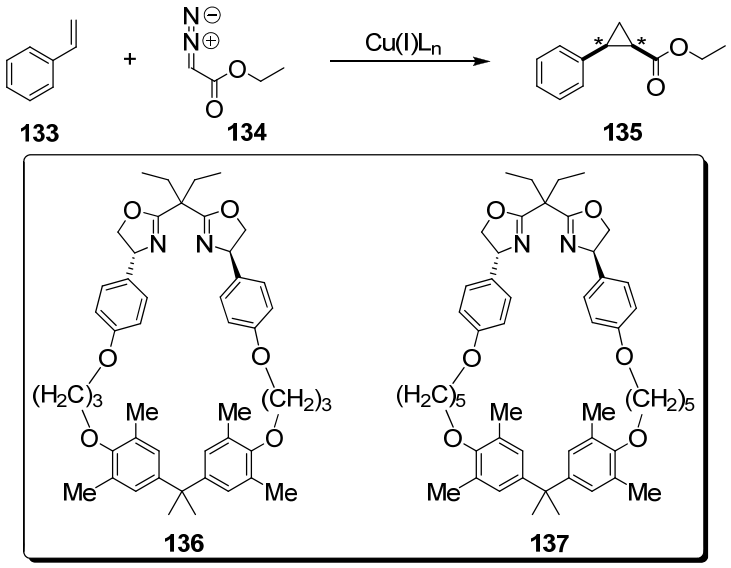
Scheme 2.2. Cyclopropanation reactions with Box ligands.[194]

Other popular reactions utilising Box ligands for asymmetric synthesis include Diels-Alder[199-202] and hetero Diels-Alder[203-206] reactions; Mukaiyama aldol[207-209] and Mukaiyama-Michael[210, 211] reactions; aziridinations;[192, 212-214] and allylic substitution reactions.[215-218] There are also some more unusual reactions[167, 219-222] and an example of a metal-free Box-mediated Diels-Alder reaction.[223] Altogether, bis(oxazoline)s are versatile ligands employed in various bond-forming reactions with a range of metal complexes available.

2.1.5. Bis(oxazoline) Macrocycles

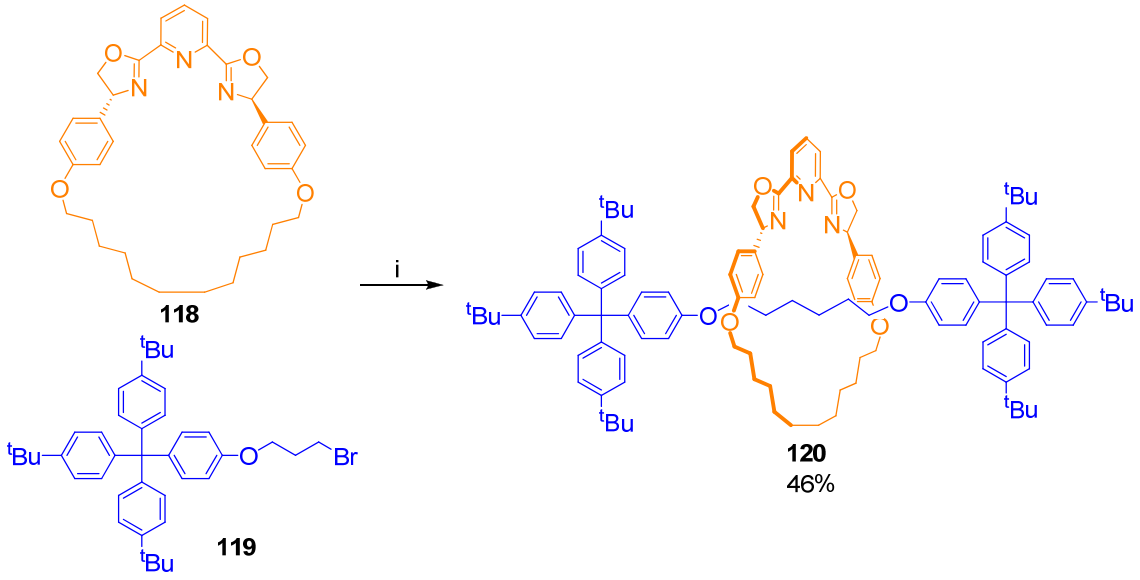
Žinić *et al.* have, to date, produced the only bidentate macrocyclic bis(oxazoline) compounds in the literature.[224] They synthesised a series of Box macrocycles and used them as chiral ligands for the copper-catalysed cyclopropanation reaction of styrene, **133** and ethyl diazoacetate **134** (Scheme 2.3). The size and flexibility of the macrocycles were found to have a significant effect on the diastereomeric outcome of the reaction: the smaller, less flexible macrocycle **136** achieved an unprecedented diastereomeric excess of 88%, with a yield of 65%; macrocycle **137**, which is larger and

more flexible, produced a better yield (78%) but a much lower de of only 48%. This link with the macrocycle cavity size and the diastereomeric selectivity of the reaction infers that the reaction is taking place *within* the cavity of the macrocycle.



Scheme 2.3. Macrocyclic Box ligands **136** and **137** for cyclopropanation of styrene **133**.[224]

During the course of our studies, a tridentate pybox macrocycle **118** was synthesised by Leigh *et al.*[155] and used in a nickel-mediated active template synthesis of rotaxane **120** (Scheme 2.4). The rotaxane produced has C_2-symmetry, as does the pybox macrocycle starting material **118**, and was obtained in a 46% yield. The use of a bis(oxazoline)-based macrocycle in an active template synthesis of a rotaxane is thus promising for the proposed asymmetric rotaxane-forming mechanism.



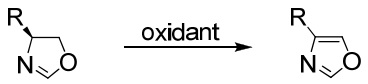
Scheme 2.4. Active template synthesis of rotaxane **120** with pybox macrocycle **118**. Reagents and conditions: (i) $NiCl_2$·DME, Zn, NMP, THF, RT. [155]

The work of Žinić and Leigh is encouraging for the proposed asymmetric synthesis of mechanically planar chiral rotaxanes, but, as yet, there are no examples of macrocyclic C_1-symmetric bis(oxazoline) compounds in the literature.

2.1.6. Removal of Point Chirality

To produce an enantiopure planar chiral rotaxane, all of the individual components must themselves be achiral. The point chirality present in bis(oxazoline)s is essential for the asymmetric active template approach to the synthesis of rotaxanes in order to provide a macrocycle with sterically different faces. However, this point chirality would produce diastereomeric rotaxanes. We must therefore be able to remove the point chirality from the Box macrocycle after the rotaxane-forming reaction in order to achieve an enantiopure rotaxane.

The choice of bis(oxazoline) as a suitable group foundation for the macrocycle was based on the possibility of removing the point chirality from the macrocycle after rotaxane formation. Oxazolines are known to undergo oxidation to the planar oxazole functionality (Scheme 2.5). The most common oxidants are nickel peroxide[225] and cupric bromide[226] and high yields can be obtained.



Scheme 2.5. Oxidation of oxazoline to oxazole, removing point chirality.

Odashima *et al.* have shown it is possible to oxidise a pyridine-bis(oxazoline) to a pyridine-bis(oxazole) in high yields using bromotrichloromethane as oxidant.[212] With this precedent the plan was to utilise this oxidation after rotaxane formation to remove the point chirality from the macrocycle and provide an enantiopure planar chiral rotaxane.

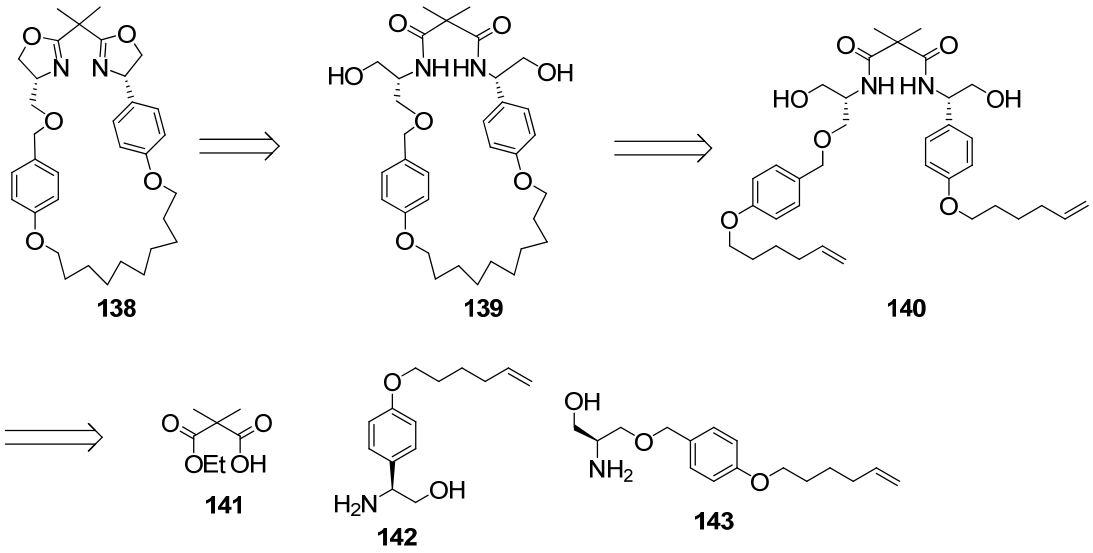
2.1.7. Summary

In order for the proposed asymmetric synthesis of mechanically planar rotaxanes to be successful, the macrocycle must possess several characteristics; namely be C_1-symeetric, have sterically different faces, posess only removable point chirality and be able to bind to a range of metals to catalyse a variety of bond-forming reactions. A bis(oxazoline)-based macrocycle would possess all of these attributes

2.2. Preparation of Macrocycle 138

2.2.1. Outline

As discussed, the macrocycle component must possess several features: complete asymmetry, sterically asymmetric faces, ability to ligate a metal and catalyse a covalent bond-forming reaction and finally, removable point chirality. Bis(oxazoline) macrocycle **138** (Scheme 2.6) has all of the attributes necessary for the proposed asymmetric synthesis of planar chiral rotaxanes. As well as this, macrocycle **138** has a cavity which should be large enough to allow metal-catalysed reactions to occur within it and the rigidity of the macrocycle should ensure that the size of the cavity remains large enough for this purpose.

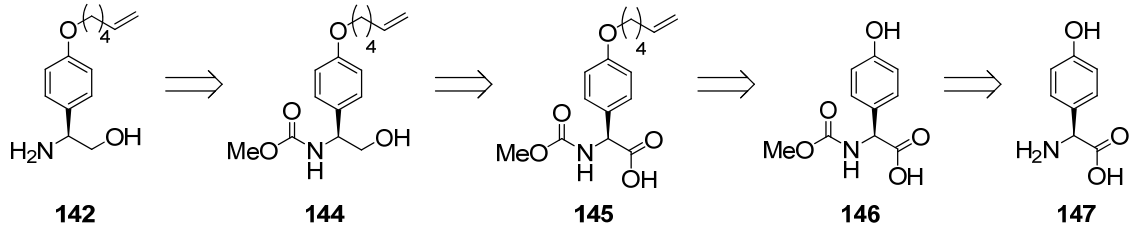


Scheme 2.6. Retrosynthetic analysis of macrocycle **138**.

Retrosynthetic analysis of macrocycle **138** is depicted in Scheme 2.6. Following standard literature procedures for the synthesis of bis(oxazoline) compounds,[155, 224] macrocycle **138** could be produced by cyclisation of macrocycle **139**. Macrocycle **139** could in turn by synthesised from unsymmetrical diene **140** using a ring closing metathesis procedure.[227] The synthesis of diene **140** could be accomplished though the coupling of amino alcohols **142** and **143** with dimethyl malonic acid monoethylester **141** following literature precedent for the formation of asymmetric bis(oxazoline) compounds.[187] Finally amino alcohols **142** and **143** could be envisaged as starting from commercially available amino acid derivatives.

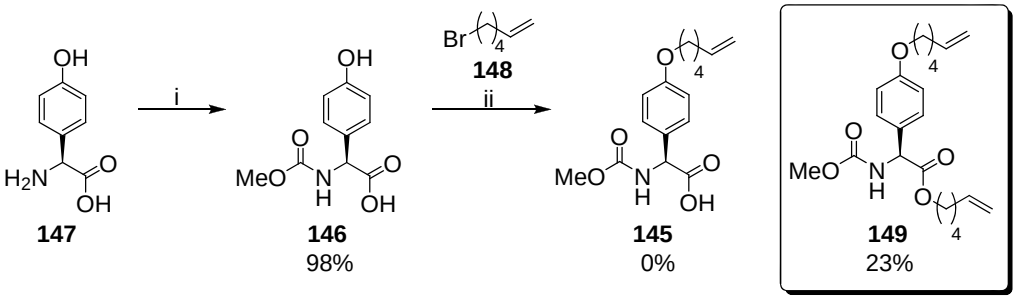
2.2.2. Synthesis of Amino Alcohol 142

Amino alcohol **142** could be synthesised from commercially available amino acid 4-hydroxy-L-phenylglycine **147** in four steps as shown in the retrosynthetic analysis (Scheme 2.7). The key steps in this transformation are the synthesis of ether **145** and its reduction to alcohol **144** with the other steps concerned with the protection/deprotection of the amine.



Scheme 2.7. Retrosynthetic analysis of amino alcohol **142**.

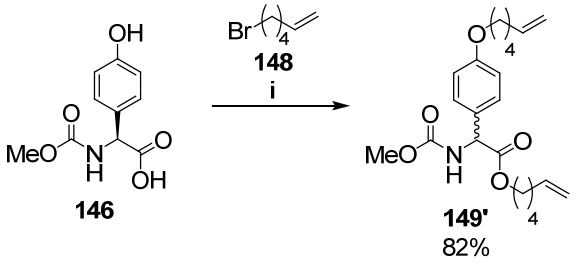
The protection of 4-hydroxy-L-phenylglycine **147** by treatment with methyl chloroformate and sodium bicarbonate was achieved in an excellent 98% yield (Scheme 2.8) following a procedure by Huang *et al.*.[228] The synthesis of ether **145** was attempted by reacting phenol **146** with potassium carbonate and 6-bromo-1-hexene **148** (Scheme 2.8). However, instead of ether **145**, diether **149** was obtained from the reaction in a 23% yield. The synthesis of diether **149** is the result of a higher than expected reactivity of the acid group of phenol **146** with bromide **148**.



Scheme 2.8. Synthesis of ether **145**. Reagents and conditions: (i) $NaHCO_3$, MeOOCCl, 1:1 THF:H_2O, RT, 22 h; (ii) **148**, K_2CO_3, acetone, reflux, 16 h.

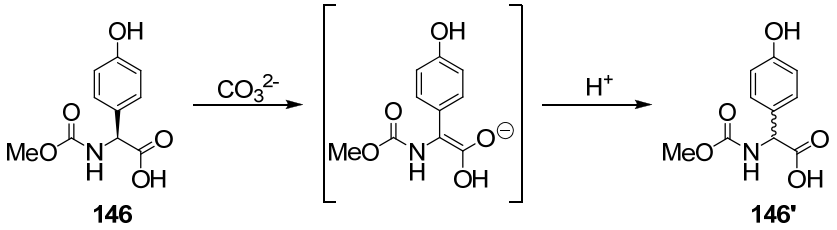
As diether **149** is a viable structure in the synthesis of amino alcohol **142**, it was decided to optimise the reaction in order to maximise the yield of diene **149** rather than to suppress its formation. In order to do this, the equivalents of bromide **148** were increased from 1 to 2.5 and the solvent was changed from acetone to acetonitrile to increase the temperature of the reaction. Following this optimisation, the yield of diether **149** was increased to 82% (Scheme 2.9). However, determination of the optical

rotation of diether **149** revealed that the compound had epimerised throughout the reaction to racemic **149'**.



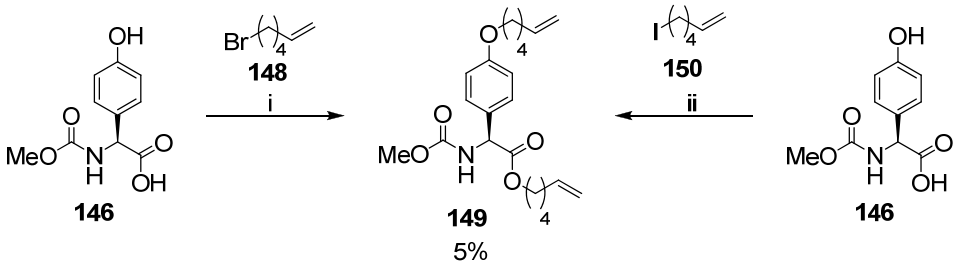
Scheme 2.9. Optimisation of diether **149'**. Reagents and conditions: (i) **148**, K_2CO_3, CH_3CN, reflux, 17 h.

Epimerisation of phenol **146** under the basic conditions occurs due to the acidity of the tertiary proton between the aromatic ring and the acid group (Scheme 2.10). Deprotonation to form a planar intermediate results in the racemisation observed.



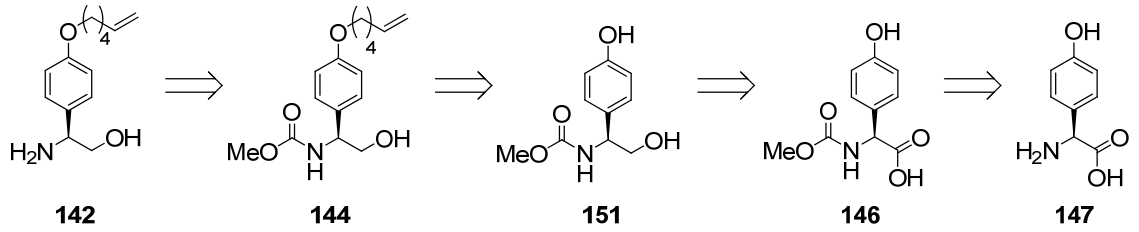
Scheme 2.10. Racemisation of phenol **146**.

Attempts were made to overcome the epimerisation of diether **149**. Initial results indicated that changing from bromide **148** to iodide **150** by the addition of sodium iodide in the reaction mixture did indeed impede epimerisation, giving a measurement for the optical rotation of the compound. However, the yield was poor; only 5% (Scheme 2.11). By pre-synthesising iodide **150**, we hoped to improve the yield of the reaction whilst retaining the benefit of non-racemisation. Unfortunately, the use of iodide **150** rather than its *in situ* synthesis had no affect on the yield of the reaction (Scheme 2.11).



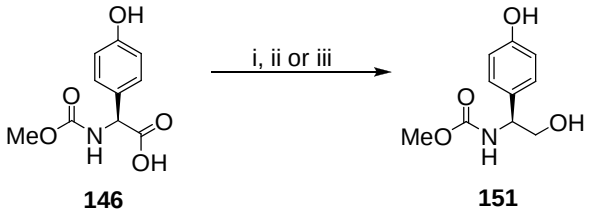
Scheme 2.11. Synthesis of non-racemic diether **149**. Reagents and conditions: (i) **148**, NaI, K_2CO_3, acetone, reflux, 26 h; (ii) **150**, K_2CO_3, acetone, reflux, 19 h.

The problem of racemisation during the synthesis of diether **149** proved difficult to overcome. Therefore, an alternative route to amino alcohol **142** from 4-hydroxy-L-phenylglycine **147** was investigated (Scheme 2.12). In this new synthetic scheme, the ether synthesis and reduction steps were reversed in order to decrease the acidity of the tertiary proton before the compound was exposed to the basic conditions required for ether synthesis. In this way, we hoped to avoid the problem of epimerisation upon ether synthesis.



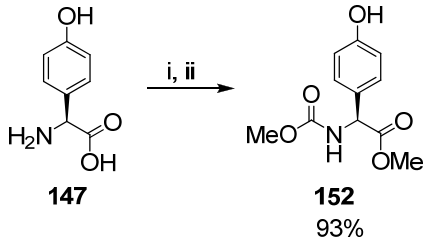
Scheme 2.12. Alternative retrosynthetic analysis for amino alcohol **142**.

Starting from the previously prepared carbamate-protected acid **146**, the reduction to alcohol **151** was attempted (Scheme 2.13). Following a procedure by Eames *et al.*,[229] acid **146** was treated with lithium aluminium hydride; but no product was obtained. $LiAlH_4$ is known to reduce carbamates to amines, although with a large excess of the reducing reagent.[230] It is possible that breakdown of the protecting group has occurred in this case. Lithium borohydride is not generally known for reduction of acids, however Organ *et al.* reported a procedure which involves transforming the acid to the acid chloride *in situ* before reduction with $LiBH_4$.[231] However, when attempted with acid **146**, no product was obtained (Scheme 2.13). Borane is considered the best reagent for the reduction of carboxylic acids to alcohols[232] and following a procedure by Klein *et al.*,[233] utilising the dimethyl sulfide complex, alcohol **151** was synthesised, but only in a 15% yield (Scheme 2.13). Again, as with the lithium aluminium hydride, this may be due to reduction of the carbamate group by the borane complex.



Scheme 2.13. Reduction of acid **146** to alcohol **151**. Reagents and conditions: (i) $LiAlH_4$, THF, reflux, 17.5 h, 0%; (ii) TMSCl, $LiBH_4$, THF, RT, 24 h, 0%; (iii) $BH_3{\cdot}SMe_3$, THF, RT, 22 h, 15%.

As the reduction of acid **146** proved to be difficult, it was decided to convert the acid to an ester at this point in the synthetic strategy in order to facilitate the reduction to the alcohol **151**. Ester **152** was synthesised from amino acid **147** in a two-step process; synthesis of the methyl ester by treatment of the acid with thionyl chloride and methanol followed by *N*-protection with sodium bicarbonate and methyl chloroformate to give ester **152** in an excellent 93% yield over two steps (Scheme 2.14).

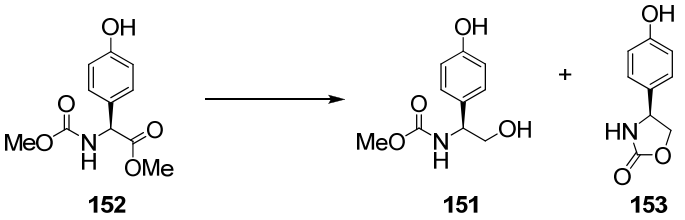


147 **152** 93%

Scheme 2.14. Synthesis of *N*-protected ester **152**. Reagents and conditions: (i) $SOCl_2$, MeOH, RT, 19 h; (ii) $NaHCO_3$, MeOOCCl, 1:1 THF:H_2O, 25 °C, 19 h.

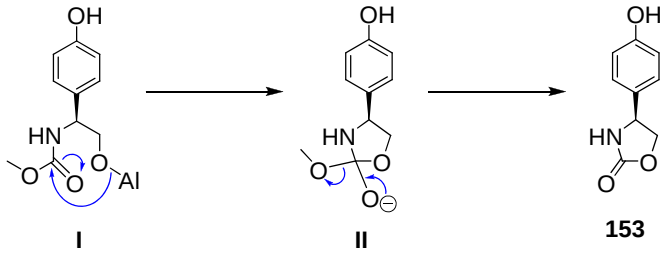
The reduction of ester **152** to alcohol **151** was then attempted (Table 2.1, entry 1). The initial reaction was carried out with lithium aluminium hydride, however, no alcohol **151** was recovered from the reaction mixture. Instead, unexpectedly, oxazolidinone **153** was retrieved in a 35% yield. **153** results from reaction of the alkoxide species produced during the reaction with the carbamate group, producing a 5-membered ring (Scheme 2.15). Changing from $LiAlH_4$ to DIBAL did result in the formation of alcohol **151** in a 19% yield, but once again the dominant product was oxazolidinone **153** (35%, Table 2.1, entry 2). Following a procedure by Sasaki *et al.*,[234] lithium borohydride was successfully used to synthesise alcohol **151** exclusively from ester **152** in a 62% yield (Table 2.1, entry 3). The difference between the aluminium-based reducing agents and lithium borohydride in the production of oxazolidinone **153** may be due to the strength of the aluminium-oxygen and boron-oxygen bonds formed during the reduction reactions (**I**, Scheme 2.15). The boron-oxygen bond is stronger by almost 300 KJ mol^{-1}.[182] Therefore, whilst the aluminium-oxygen bond may be broken in favour of the formation of a 5-membered ring, the boron-oxygen bond is too strong for this to occur.

Table 2.1. Reduction of Ester **152**



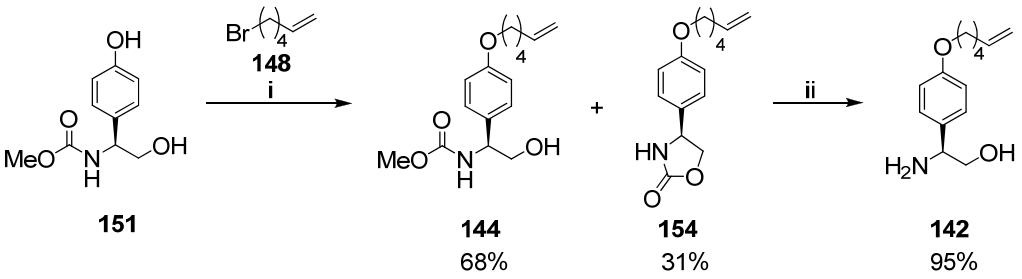
Entry	Reducing Agent	Yield of **151** (%)	Yield of **153** (%)
1[a]	$LiAlH_4$	0	35
2[b]	DIBAL	19	36
3[c]	$LiBH_4$	62	0

[a] Reagents and conditions: $LiAlH_4$, THF, RT, 18 h. [b] Reagents and conditions: DIBAL, THF, 30 °C, 120 h. [c] Reagents and conditions: $LiBH_4$, THF, 25 °C, 66.5 h, 40 °C, 43.5 h.



Scheme 2.15. Mechanism for oxazolidinone formation.

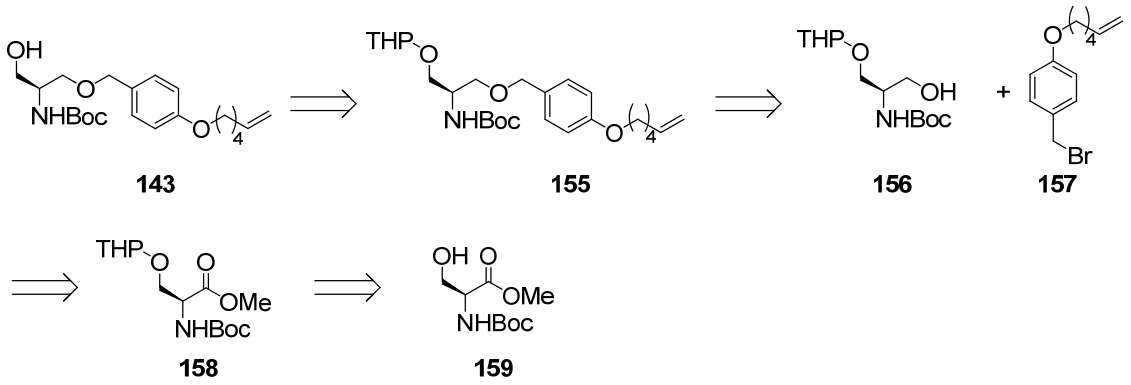
Phenol **151** was then treated with potassium carbonate and 6-bromo-1-hexene **148** in acetone resulting in ether **144** and oxazolidinone **154** in almost quantitative yield (99%). **154** results from the same alkoxide reaction with the carbamate *N*-protecting group as seen in the formation of oxazolidinone **153** under reduction conditions (Scheme 2.15). However, ethers **144** and **154** can both be treated with potassium hydroxide at 50 °C in the same reaction to successfully provide amino alcohol **142** in a 95% yield.



Scheme 2.16. Synthesis of amino alcohol **142**. Reagents and conditions: (i) **148**, K_2CO_3, acetone, reflux, 42.5 h; (ii) KOH, H_2O, 50 °C, 27 h.

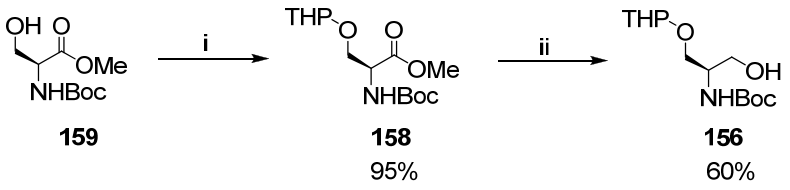
2.2.3. Synthesis of Amino Alcohol 143

Retrosynthetic analysis of amino alcohol **143** indicates that it can be synthesised from commercially available Boc-L-serine methyl ester **159** in four steps (Scheme 2.17). The key steps are the reduction of ester **158** and the synthesis of ether **155** from alcohol **156** and bromide **157**.



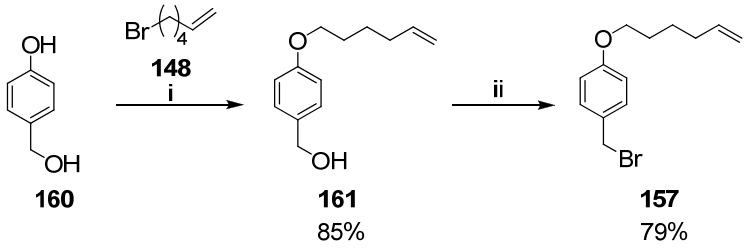
Scheme 2.17. Retrosynthetic analysis of amino alcohol **143**.

The first step in the synthesis of amino alcohol **143** is the alcohol group protection of Boc-L-serine methyl ester **159** which is readily accomplished by treatment with dihydropyran and pyridinium *p*-toluenesulfonate in dichloromethane, resulting in the THP-protected ester **158** in good yield (95%, Scheme 2.18).[235] Subsequent reduction of ester **158** with DIBAL in toluene provided alcohol **156** in a reasonable 60% yield.[236]



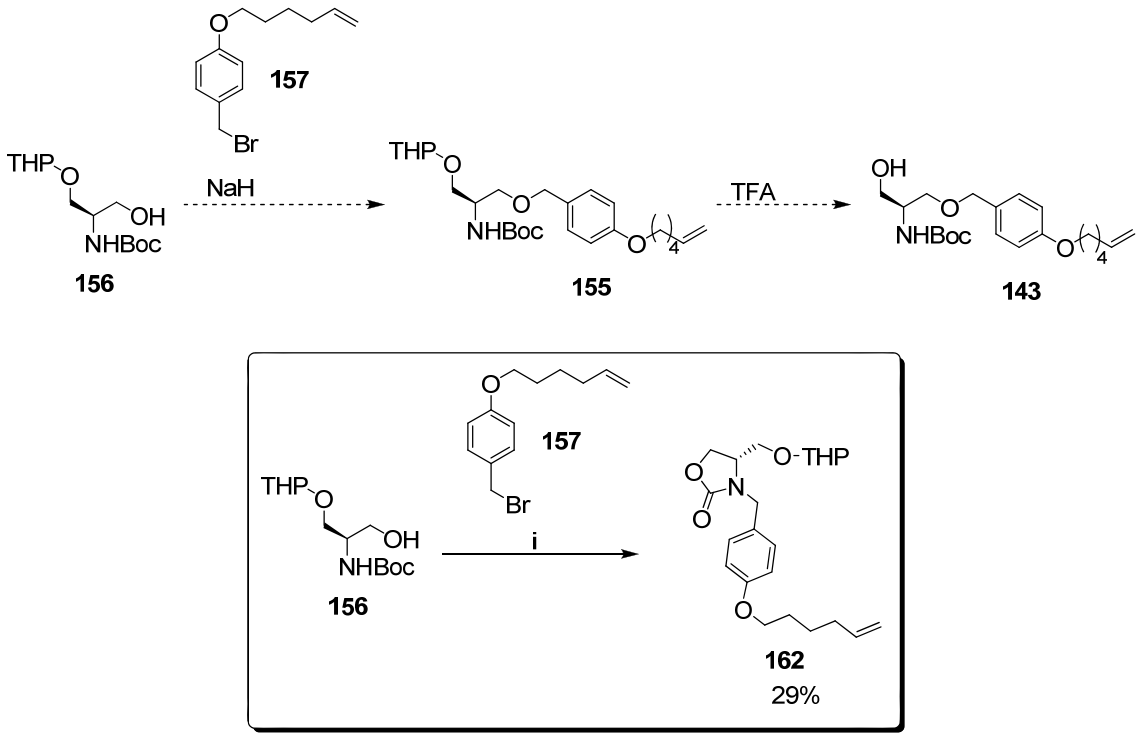
Scheme 2.18. Synthesis of alcohol **156**. Reagents and conditions: (i) DHP, PyH·OTs, DCM, 25 °C, 20 h; (ii) DIBAL, toluene, 0 °C, 3 h, 25 °C, 20 h.

The next step in the synthesis of amino alcohol **143** is the etherification of alcohol **156** with bromide **157** to produce ether **155**. Bromide **157** is prepared from commercially available 4-hydroxybenzyl phenol **160** in two steps (Scheme 2.19). Alkylation of **160** with 6-bromo-1-hexene **148** yields ether **161** in an 85%.[237] Bromination of alcohol **161** by treatment with phosphorous tribromide in dichloromethane gives bromide **157** in a 79% yield. Bromide **157** is unstable to silica column chromatography and so was carried on crude.



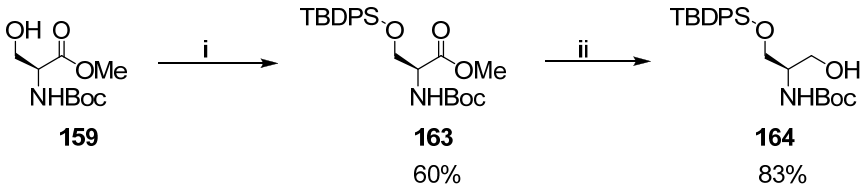
Scheme 2.19. Synthesis of bromide **157**. Reagents and conditions: (i) **148**, K_2CO_3, acetone, reflux, 49 h; (ii) PBr_3, DCM, dark, RT, 17 h.

The intended scheme from alcohol **156** to amino alcohol **143** is depicted in Scheme 2.20. Etherification of alcohol **156** with bromide **157** using sodium hydride should provide ether **155** which should by easily deprotected in one step by treatment with trifluoroacetic acid to give amino alcohol **143**. However, reaction of **156** with sodium hydride and bromide **157** did not produce the expected ether **155** but the *N*-alkylated oxazolidinone **162** instead (Scheme 2.20). This results from a similar mechanism as the formation of oxazolidinones **153** and **154** (Scheme 2.15), with the alkylation of the amide occurring subsequently. Unfortunately, unlike with oxazolidinones **153** and **154**, *N*-alkylated **162** cannot be used in the synthesis of amino alcohol **143**.



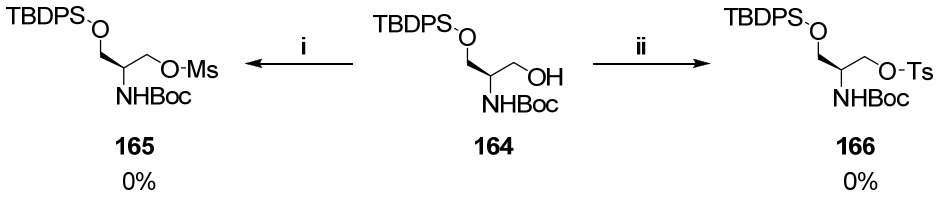
Scheme 2.20. Synthesis of oxazolidinone **162**. Reagents and conditions: (i) NaH, **157**, THF, 25 °C, 16 h.

In order to circumvent the problem of oxazolidinone formation in the synthetic scheme for amino alcohol **143**, various different routes were attempted. In order to simplify the elucidation of the structures produced, it was decided to change protecting groups from tetrahydropyran, which results in diasteromeric compounds due to its chiral centre, to the non-chiral *tert*-butyldiphenylsilyl. This was achieved by reaction of Boc-L-serine methyl ester **159** with *tert*-butyldiphenylsilyl chloride and imidazole to give TBDPS-protected ester **163** in a 60% yield (Scheme 2.21).[238] Reduction of ester **163** with lithium borohydride gave alcohol **164** in a good yield (83%).[238]



Scheme 2.21. Synthesis of alcohol **164**. Reagents and conditions: (i) TBDPSCl, imidazole, DCM, RT, 17 h; (ii) $LiBH_4$, THF, RT, 89 h.

By converting alcohol **164** into either a mesylated, **165**, or tosylated, **166**, compound and reacting this with alcohol **161** under standard ether conditions we believed it would be possible to prevent cyclisation to the oxazolidinone. Attempts to form either of these compounds, however, proved unsuccessful (Scheme 2.22).



Scheme 2.22. Attempted synthesis of mesylate **165** and tosylate **166** Reagents and conditions: (i) MsCl, Et_3N, DCM, 0 °C, 30 min, RT, 18 h; (ii) TsCl, Et_3N, DCM, 0 °C, RT, 18 h.

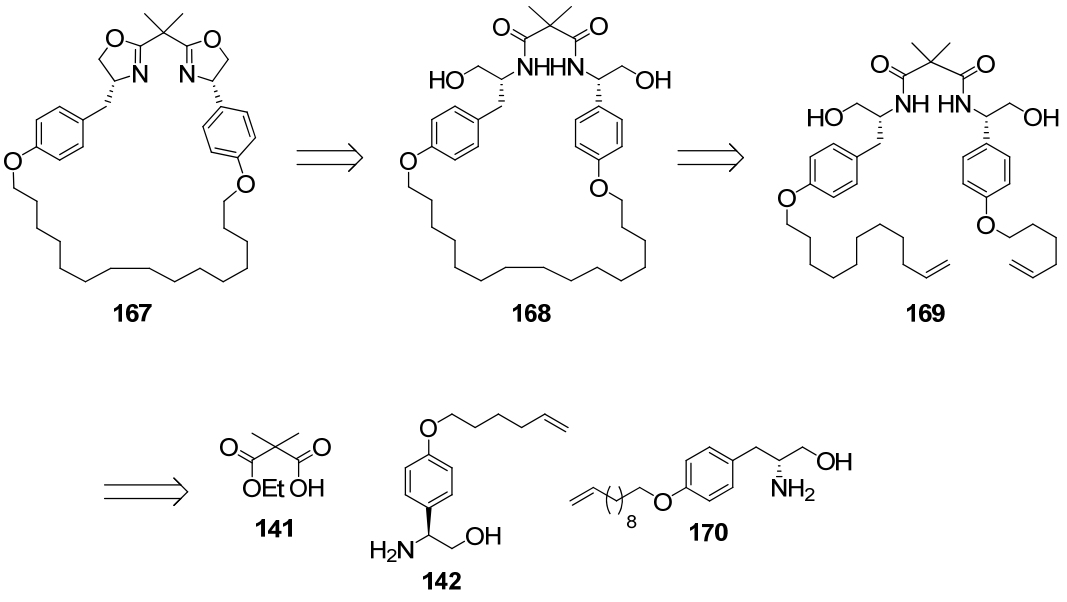
After various failed attempts at circumventing the problem of oxazolidinone formation on the route towards amino alcohol **143** the macrocycle design was revisited in order to determine if a new synthetic scheme would be possible.

2.3. Preparation of Macrocycle 167

2.3.1. Outline

Due to the inability to synthesise amino alcohol **143** the synthetic scheme to macrocycle **138** was scrutinised. However, no alternative synthesis to macrocycle **138** without amino alcohol **143** was forthcoming. Therefore, a new bis(oxazoline) macrocycle had to be designed which avoided the same oxazolidinone formation problem. The new bis(oxazoline) macrocycle still had to fulfil the same requirements as macrocycle **138**, namely be completely asymmetric with a cavity size large enough for the metal-catalysed bond-forming reaction to occur within it, and with a certain amount of rigidity for this to be the case. Also, the macrocycle should incorporate previously synthesised amino alcohol **142** and a new amino alcohol which could be easily synthesised from a commercially available amino acid derivative.

Macrocycle **167** was designed as an alternative to macrocycle **138** (Scheme 2.23). As before, retrosynthetic analysis shows macrocycle **167** can be synthesised with standard procedures from diol macrocycle **168**. Again, this can be synthesised by a ring closing metathesis procedure from unsymmetrical diene **169**. This in turn can be synthesised from the already prepared amino alcohol **142** by coupling with dimethyl malonic acid monoethylester **141** and amino alcohol **170** which is derived from a commercially available tyrosine derivative.

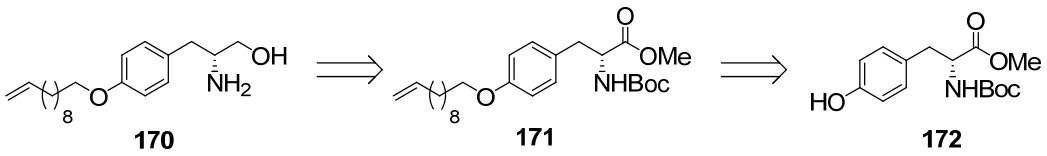


Scheme 2.23. Retrosynthetic analysis of macrocycle **167**.

Macrocycle **167** has much of the same properties as the original macrocycle **138**, the presence of the Box moiety for the rotaxane-forming reaction key amongst them. However, it was noted that macrocycle **167** is less rigid than the original design and this may affect the ability of the macrocycle to form rotaxanes. Nevertheless, due to the problems encountered in the synthesis of macrocycle **138** we decided to attempt the formation of macrocycle **167** and to apply it to the attempted synthesis of rotaxanes.

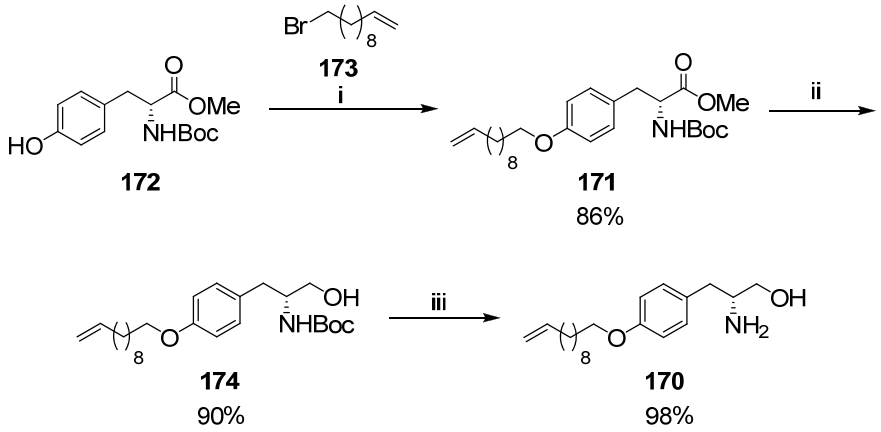
2.3.2. Synthesis of Amino Alcohol 170

Retrosynthetic analysis of amino alcohol **170** is shown in Scheme 2.24 . Amino alcohol **170** can be produced from commercially available Boc-D-tyrosine methyl ester **172** through alkylation, reduction and deprotection, in that order.



Scheme 2.24. Retrosynthetic analysis of amino alcohol **170**.

Boc-D-tyrosine methyl ester **172** underwent alkylation with 11-bromo-1-undecene **173** in acetonitrile to provide ether **171** in an 86% yield (Scheme 2.25). Subsequent treatment of ether **171** with lithium borohydride to reduce the ester furnished alcohol **174** with a 90% yield. Removal of the *N*-protecting Boc group yielded amino alcohol **170** in almost quantitative yield (98%) on a 14 g scale.

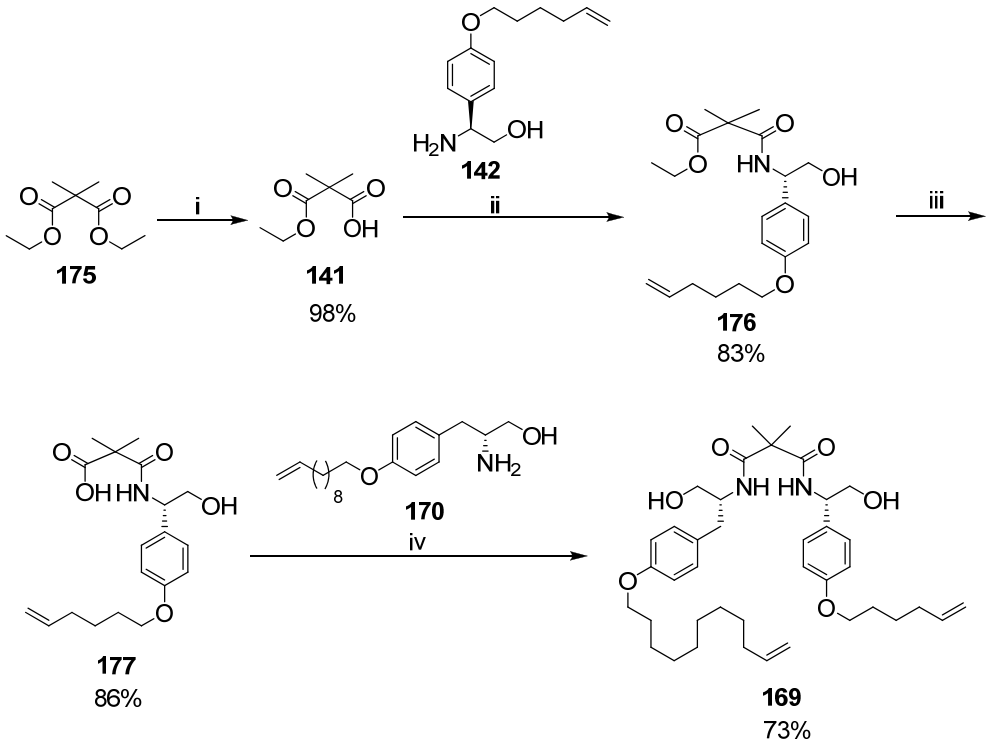


Scheme 2.25. Synthesis of amino alcohol **170**. Reagents and conditions: (i) **173**, K_2CO_3, MeCN, reflux, 23 h; (ii) $LiBH_4$, THF, 25 °C, 43 h; (iii) *p*-TsOH·H_2O, 1:1 THF:DCM, reflux, 23 h.

2.3.3. Synthesis of Macrocycle 167

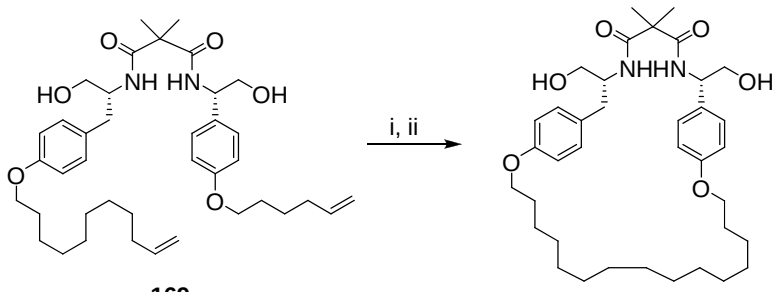
With both amino alcohols **142** and **170** in hand, assembly of macrocycle **167** could commence. An ethanol solution of commercially available diethyl dimethylmalonate **175** was treated with sodium hydroxide for 2 hours at 40 °C to provide dimethyl malonic acid monoethylester **141** in a 98% yield (Scheme 2.26).[239] Coupling of acid **141** with amino alcohol **142** to provide amide **176** in an 83% yield was achieved with an EDCI-promoted reaction in chloroform with the addition of HOBt as a racemisation inhibitor.[187] Hydrolysis of ester **176** with sodium hydroxide at 40 °C afforded acid **177** (86%).

The coupling of acid **177** with amino alcohol **170** was initially attempted under the same conditions as the coupling of **141** with **142**, resulting, however, in a low yield (19%) of diamide **169** (Scheme 2.26). This was significantly increased to 48% by the addition of an excess of triethylamine to the reaction. Changing amide coupling reagent from EDCI to TBTU with DIPEA as excess amine improved the yield of diamide **169** to 73%. Synthesis of unsymmetrical diene **169** was therefore achieved on a 4 g scale in reasonable yield.



Scheme 2.26. Synthesis of diol **168**. Reagents and conditions: (i) NaOH, EtOH, 40 °C, 3 h; (ii) **142**, EDCI, HOBt, $CHCl_3$, RT, 18 h; (iii) NaOH, 1:1 THF:H_2O, 40 °C, 3 h; (iv) **170**, TBTU, DIPEA, 4:1 DCM:DMF, RT, 92 h.

The transformation from unsymmetrical diene **169** to macrocycle **168** was completed in two steps (Scheme 2.27). Initial macrocyclisation was achieved by treatment of diene **169** with Grubbs' 1st generation olefin metathesis catalyst[135] in dichloromethane under high dilution conditions (0.003 M). The choice of Grubbs' 1st generation catalyst was based on literature precedence for the use of this catalyst in macrocycle synthesis.[139, 227, 237, 240] A trial reaction was carried out with Hoveyda-Grubbs' 2nd generation catalyst,[241] but it proved less effective in the reaction than the chosen catalyst. The reaction proved sluggish and was heated at reflux for 7 days in order to obtain a reasonable conversion from diene **169**. The product from the reaction was purified to remove unreacted **169** then subjected to a hydrogen atmosphere after the addition of palladium on activated charcoal to reduce the remaining carbon double bond and produce macrocycle **168**. Conversion of unsymmetrical diene **169** to macrocycle **168** was achieved in a reasonable 65%. The reaction was limited to a 2 g scale (producing 1 g of **168**) due to the requirement for high dilution in the first step.

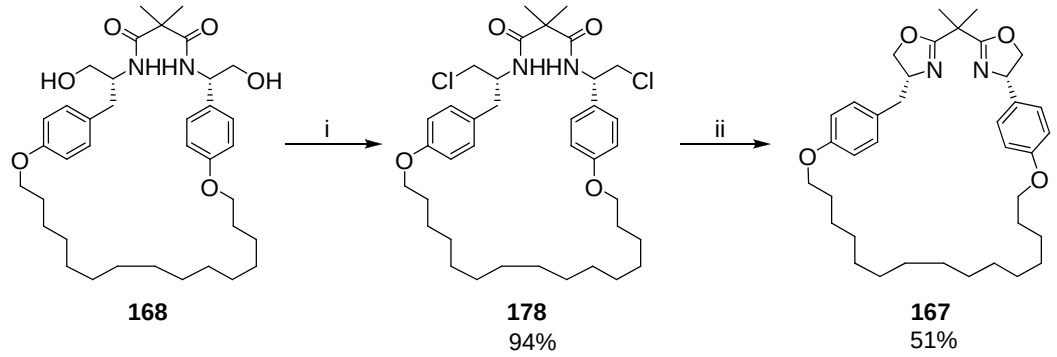


169 **168**
65%

Scheme 2.27. Synthesis of macrocycle **168**. Reagents and conditions: (i) Grubbs 1st generation catalyst, DCM, reflux, 7 days; (ii) 10% w/w Pd/C, THF, H_2, RT, 6 h.

Dichloride **178** was synthesised by the reaction of diol **168** with thionyl chloride in dichloromethane in a high 94% yield and proved to be surprisingly stable (Scheme 2.28). The target macrocycle **167** was then synthesised by the TBAF-promoted cyclisation of the amide and chloride moieties to form the bis(oxazoline) group in a 51% yield.[155] Box macrocycle **167** proved unstable to silica chromatography, reverting to diol macrocycle **168**. Optimisation of column chromatography techniques was carried out, with attempts at buffered silica columns and reverse-phase coated silica, and eventually a buffered neutral alumina column chromatography technique was developed for purification.

The synthetic procedure towards diol **169** was later improved and scaled up to mutli-gram scale by the Lee group, providing gram quantities of macrocycle **167**.[242]



168 **178** 94% **167** 51%

Scheme 2.28. Synthesis of macrocycle **167**. Reagents and conditions: (i) $SOCl_2$, DCM, RT, 23 h; (ii) TBAF, DCM, RT, 43 h.

2.4. Summary and Conclusion

In conclusion, the synthesis of the first C_1-symmetric bis(oxazoline) macrocycle was achieved on a 1 g scale. Although not the initial macrocycle designed for the asymmetric active template methodology for rotaxane synthesis, macrocycle **167** possess all of the characteristics identified for success in the attempts at the asymmetric synthesis of a mechanically planar chiral rotaxane.

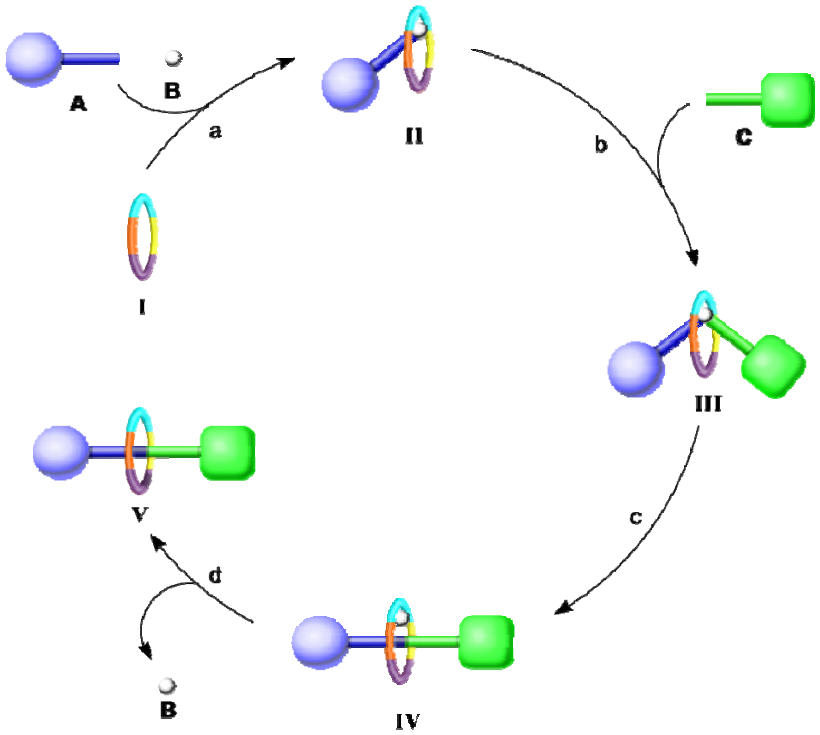
Chapter 3
Studies Towards Rotaxane Synthesis

James O'Neill is gratefully acknowledged for his contribution to the study of the Cadiot-Chodkiewicz reaction for rotaxane formation (Table 3.1).

Chapter 3: Studies Towards Rotaxane Synthesis

3.1. Introduction

The proposed asymmetric synthesis of mechanically planar chiral rotaxanes discussed in Chapter 1 (Scheme 3.1) requires a suitable bond-forming reaction to couple the stopper fragments together within the macrocycle. The reaction must be capable of *hetero*coupling two distinct half-threads, whilst the coordination geometry of the metal centre ensures the reaction takes place *through* the macrocycle cavity. Of the various reactions used to date in the active template synthesis of rotaxanes, the Cadiot-Chodkiewicz heterocoupling reaction, the oxidative Heck reaction and the CuAAC 'click' reaction are the most promising for use in the asymmetric synthesis of rotaxanes. They have been shown to produce rotaxanes in high yield using the active metal template approach and have the capacity to produce directionality in threads. As bis(oxazoline) ligands are not known in these reactions, investigations into their possible use for the asymmetric synthesis of rotaxanes must begin with studies into the application of Box ligands in these reactions.



Scheme 3.1. Proposed asymmetric active template for rotaxane formation. a) Approach of first half-thread **A** and metal **B** to less sterically hindered face of asymmetric macrocycle **I**. b) Approach of second half-thread **C** to species **II** to give species **III**. c) Covalent bond-forming reaction to form rotaxane **IV**. d) Removal of metal to furnish planar chiral rotaxane **V**.

3.2. Macrocycle Substitutes

Since only pyridine and/or bipyridine-based macrocycles have been utilized in these rotaxane forming reactions, and Box ligands have either not been evaluated (Cadiot-Chodkiewicz, CuAAC 'click') or have only seen limited study (oxidative Heck),[243, 244] it was necessary to carry out model studies in order to understand how bis(oxazoline) ligands will perform in these reactions.

As macrocycle **167** is precious, initially model Box ligands were required. Thus, commercially available non-macrocyclic C_2-symmetric Box ligands **179** and **180** were utilized in these investigations. However, a C_1-symmetric model compound with similar substituents to macrocycle **167**, namely one phenyl and one benzyl group, was also required for comparison purposes. Box compound **181** was therefore synthesised as a C_1 non-macrocyclic model for the investigations.

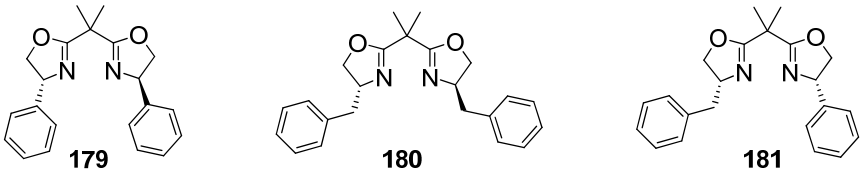
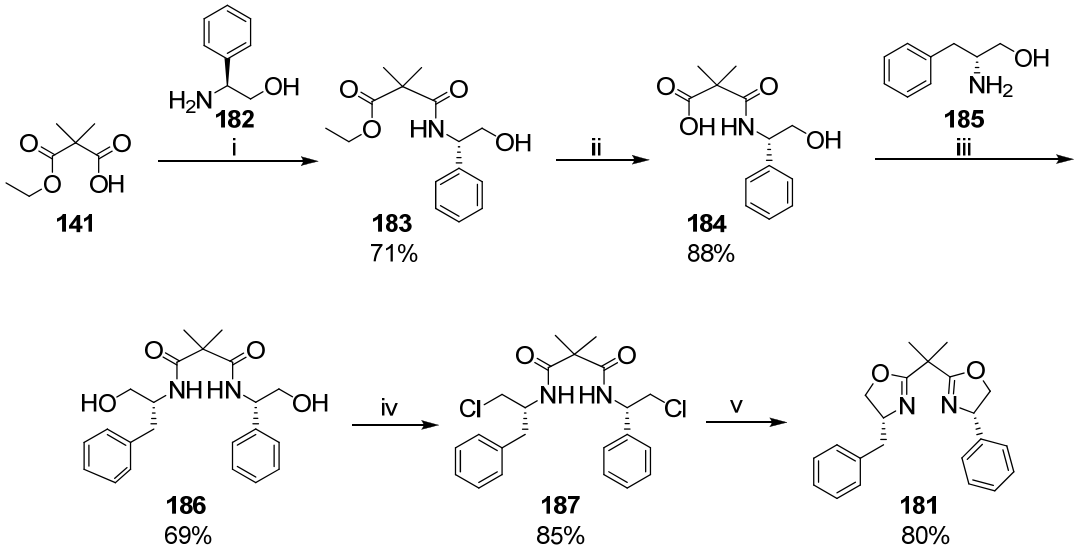


Figure 3.1. Substitutes for Box macrocycle **167**.

3.2.1. Synthesis of Non-Macrocyclic C_1-Box Ligand 181

Synthesis of model non-macrocyclic C_1-bis(oxazoline) **181** was carried out following the same route as for bis(oxazoline) macrocycle **167** (Scheme 3.2). Coupling of commercially available (*S*)-2-phenylglycinol **182** with dimethyl malonic acid monoethylester **141** in an EDCI-promoted amide coupling with the addition of HOBt as a racemisation inhibitor produced amide **183** in a 70% yield.[245] Treatment of ester **183** with sodium hydroxide at 40 °C resulted in the formation of acid **184** in an 82% yield.[187] Coupling of acid **184** with commercially available D-phenylalaninol **185** in another EDCI-promoted amide coupling, this time with the addition of an excess of triethylamine, gave a 69% yield of diamide **186**. Dichloride **187** was prepared from diol **186** using thionyl chloride in a good 85% yield and subsequent treatment of dichloride **187** with TBAF resulted in cyclisation to bis(oxazoline) **181** in an 80% yield.[155] Thus non-macrocycle C_1-Box ligand **181** was synthesised for use in the model rotaxane formation studies.

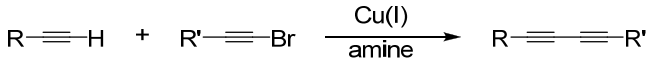


Scheme 3.2. Synthesis of model C_1-symmetric Box ligand **181**. Reagents and conditions: (i) **182**, EDCI, HOBt, $CHCl_3$, RT, 21 h; (ii) NaOH, 1:1 THF:H_2O, 40 °C, 2.5 h; (iii) **185**, EDCI, HOBt, Et_3N, $CHCl_3$, RT, 41 h; (iv) $SOCl_2$, DCM, RT, 19 h; (v) TBAF, THF, RT, 18 h.

3.3. Cadiot-Chodkiewicz Heterocoupling Reaction

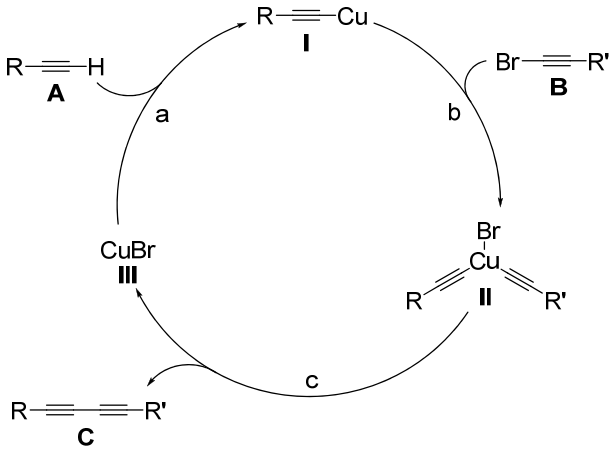
3.3.1. Introduction

The Cadiot-Chodkiewicz reaction produces non-symmetrical diynes through the copper-mediated coupling of acetylenes and bromoacetylenes in the presence of an amine (Scheme 3.3).[246-248] The reaction is well known[249] and tolerates a range of functional groups including amines,[250-253] alcohols,[251, 253-261] epoxides,[262] esters,[262] amides,[263] carboxylic acids,[264] disulfides[254] and transition metal complexes.[265]



Scheme 3.3. Cadiot-Chodkiewicz heterocoupling of acetylene and bromoacetylene.

The proposed reaction mechanism of the Cadiot-Chodkiewicz reaction is shown in Scheme 3.4.[266] The first step of the reaction is the formation of the reactive intermediate, the copper-acetylide **I** (a, Scheme 3.4). Oxidative addition of the bromoalkyne **B** to copper-acetylide **I** then forms a Cu(III) species **II** (b, Scheme 3.4). The dialkyne product **C** is formed *via* a reductive elimination, which also regenerates the Cu(I) catalyst **III** (c, Scheme 3.4).



Scheme 3.4. Proposed mechanism of the Cadiot-Chodkiewicz heterocoupling reaction. a) Ligand exchange. b) Oxidative addition. c) Reductive elimination.[266]

Cadiot-Chodkiewicz Reaction in Supramolecular Chemistry

As well as its use in the total synthesis of various natural products which contain polyacetylene functionality,[258, 260-263] the Cadiot-Chodkiewicz reaction has been used in the field of supramolecular chemistry. Kozhushkov and de Meijere have used the heterocoupling reaction in the formation of macrocyclic oligodiacetylenes (**188**, Figure 3.2)[267] and Bunz *et al.* utilised the reaction in the synthesis of unusual cyclynes with dicycle and 'butterfly' topologies (**189** and **190**, Figure 3.2).[268, 269]

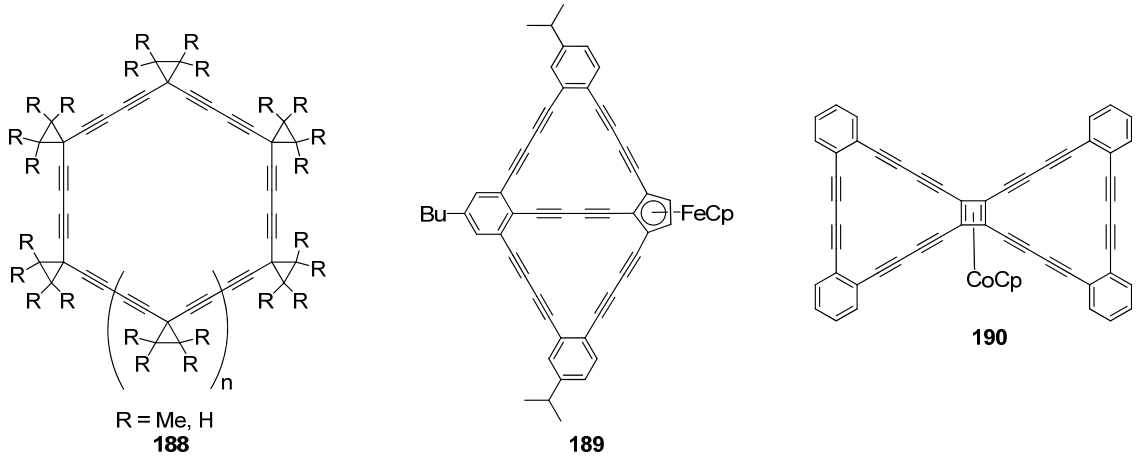
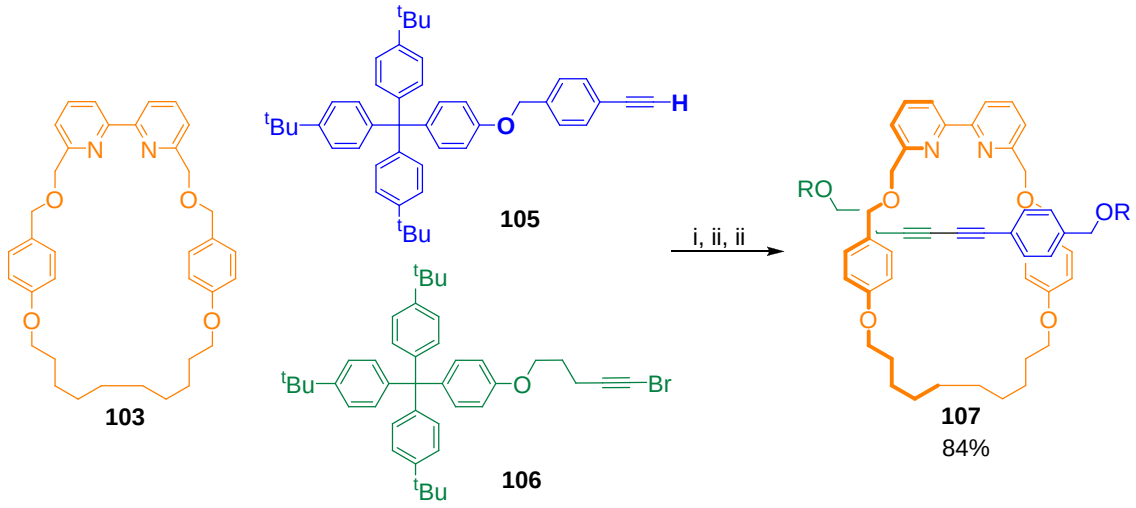


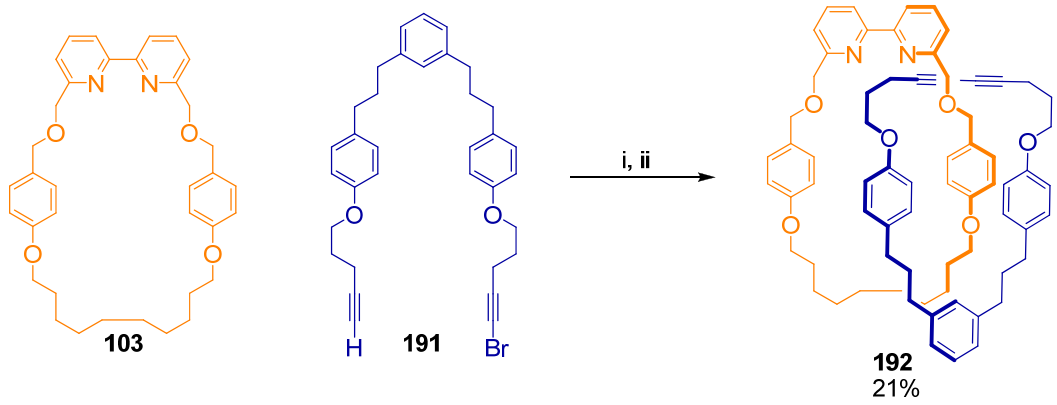
Figure 3.2. Oligodiacetylene macrocycle (**188**),[267] dicyclyne **(189)**[268] and 'butterfly' **(190)**[269] topologies.

Leigh and co-workers have used the Cadiot-Chodkiewicz reaction in their active metal synthesis of rotaxanes and catenanes.[152, 270] Although standard conditions provided them with rotaxane **107**, problems with the selectivity between the heterocoupling and homocoupling reactions lead to a modified reaction. Synthesis of the copper-acetylide reactive intermediate was carried out with *n*-butyl lithium before addition of the

bromoacetylene **106**, resulting in a greater than 98% selectivity for the desired rotaxane **107** and with an 84% yield (Scheme 3.5).[152] These reaction conditions were also used in the active template synthesis of catenane **192**, providing it in a 21% yield (Scheme 3.6).[270]



Scheme 3.5. Cadiot-Chodkiewicz active metal synthesis of rotaxane **107**. Reagents and conditions: (i) n-BuLi, **105**, THF, -78 °C → 0 °C, 15 min; (ii) CuI, 0 °C → RT, 15 min; (iii) **103**, **106**, THF, -78 °C → RT, 20 h.[152]

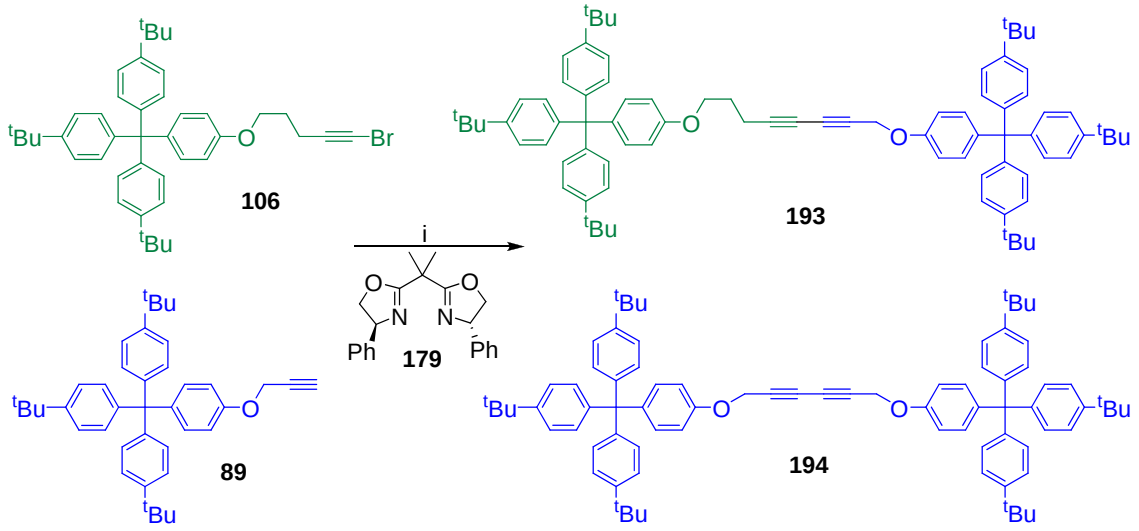


Scheme 3.6. Cadiot-Chodkiewicz active metal synthesis of catenane **192**. Reagents and conditions: (i) LiHMDS, **103**, THF, -78 °C, 30 min; (ii) CuI, **191** (5 eq.), 80 °C, 72 h.[270]

These active template syntheses of both catenanes and rotaxanes with the Cadiot-Chodkiewicz heterocoupling reaction are the basis for the trial of the reaction in the asymmetric active metal synthesis of rotaxanes.

3.3.2. Suitability of Box Ligands in the Cadiot-Chodkiewicz Reaction

In order to determine if bis(oxazoline)s are suitable ligands in the copper (I)-catalysed Cadiot-Chodkiewicz heterocoupling of acetylenes, a trial reaction was carried out based on the reaction conditions developed by Leigh *et al.* for rotaxane synthesis with bipyridine macrocycles (Scheme 3.7).[152]



Scheme 3.7. Cadiot-Chodkiewicz heterocoupling trial with Box ligand **179**. Reagents and conditions: (i) *n*-BuLi, CuI, THF, RT, 20 h, conversion 46%, **193**:**194** 60:40.

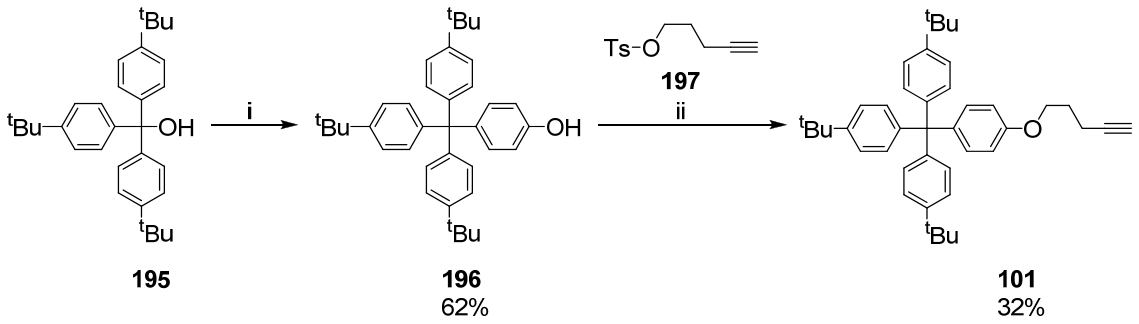
Treatment of acetylene **89** with *n*-butyl lithium at -78 °C, addition of CuI at 0 °C and subsequent addition of bromide **106** and C_2-Box ligand **179** at -78 °C followed by reaction at room temperature overnight gave a conversion of acetylene **89** to heterocoupled thread **193** and homocoupled thread **194** of 46% and a ratio of **193** to **194** of 60:40. This conversion is low in comparison with the bipyridine macrocycle mediated rotaxane-forming reaction of Leigh *et al.* which produced rotaxane in a 74% yield with these stoppers and conditions.[152] Also, the presence of homocoupled threads, either from the acetylene or bromide stoppers, was not observed by Leigh *et al.* using the bipyridine macrocycle with the conditions trialled. However, the successful production of heterocoupled thread **193** with a bis(oxazoline) ligand indicates that the reaction is viable for the asymmetric rotaxane-forming reaction.

3.3.3. Non-symmetric Stoppers for the Cadiot-Chodkiewiz Reaction

Although the stoppers developed by Leigh *et al.*[152] for the Cadiot-Chodkiewicz formation of rotaxanes are different and do produce a non-symmetric thread, they are structurally similar, with only the length of the carbon chain between the ether group

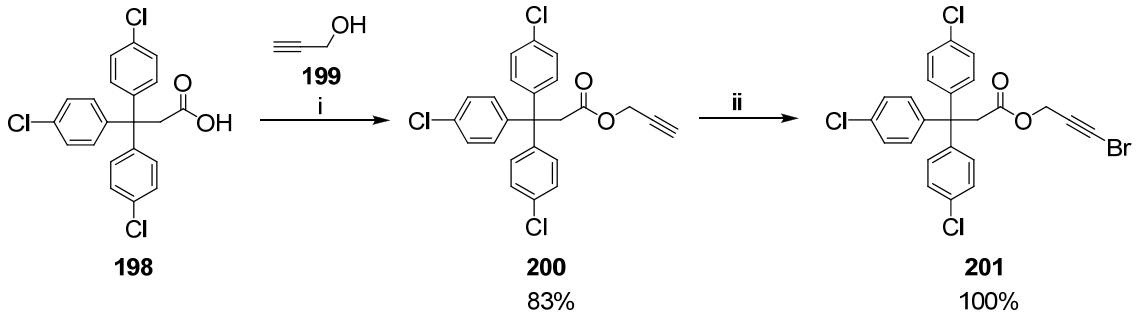
and the acetylene linker differing on each side. In order to emphasise the asymmetry of any planar chiral rotaxanes produced, half-threads with significantly different stopper groups were designed for the Cadiot-Chodkiewicz reaction.

Acetylene **101** was utilised as a stopper for the Cadiot-Chodkiewicz active template synthesis of rotaxanes by Leigh[152] and was synthesised following literature procedures (Scheme 3.8).[43, 271] Tris(*p-tert*-butyl-phenyl)methanol **195** reacted with phenol and a catalytic amount of hydrochloric acid to produce 4-[tris-(*p-tert*-butyl-phenyl)-methyl]phenol **196** in a 62% yield. Treatment of phenol **196** with potassium carbonate and pent-4-ynyl 4-methylbenzenesulfonate **197** gave acetylene **101** in a 32% yield.



Scheme 3.8. Synthesis of acetylene stopper **101**. Reagents and conditions: (i) Phenol, 35% aq. HCl, reflux, 19.5 h; (ii) **197**, K_2CO_3, 18-crown-6, butanone, reflux, 90 h.

The starting point for the synthesis of bromide stopper **201** is commercially available 3,3,3-tris(4-chlorophenyl)propanoic acid **198**. Coupling of acid **198** with propargyl alcohol **199** in an EDCI-promoted reaction yields acetylene **200** (83%, Scheme 3.9). Subsequent treatment of acetylene **200** with silver nitrate and *N*-bromosuccinimide in a light-protected flask gave bromide stopper **201** in quantitative yield.



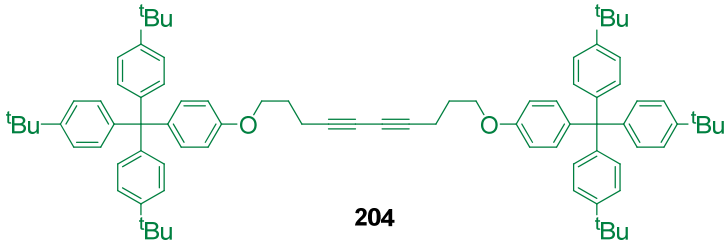
Scheme 3.9. Synthesis of bromide stopper **201**. Reagents and conditions: (i) **199**, EDCI, DMAP, DCM, RT, 5 h; (ii) $AgNO_3$, NBS, acetone, RT, dark, 1 h.

3.3.4. Cadiot-Chodkiewicz Reaction Trials

With the new stoppers for the Cadiot-Chodkiewicz heterocoupling reaction in place, optimisation of the reaction for bis(oxazoline) ligands could begin. Initial optimisation was carried out using commercially available C_2-symmetric bis(oxazoline) **179**.

Optimisation with C_2-Box ligand 179

The first reaction with C_2-Box ligand **179** in the formation of heterocoupled thread **202** (Table 3.1, entry 1) was carried out using the same conditions as for the formation of thread **193** (Scheme 3.7). To our surprise, the reaction resulted in a conversion from bromide **201** to threads **202** and **203** of 70%, significantly higher than the 46% obtained in the formation of **193**, with a ratio of heterocoupled, **202**, to homocoupled, **203**, thread of 60:40. Homocoupled acetylene **204** (Figure 3.3) was also found to be present, but was unquantifiable due to overlapping peaks in the ^{1}H NMR spectrum in the area where the peaks could be observed.

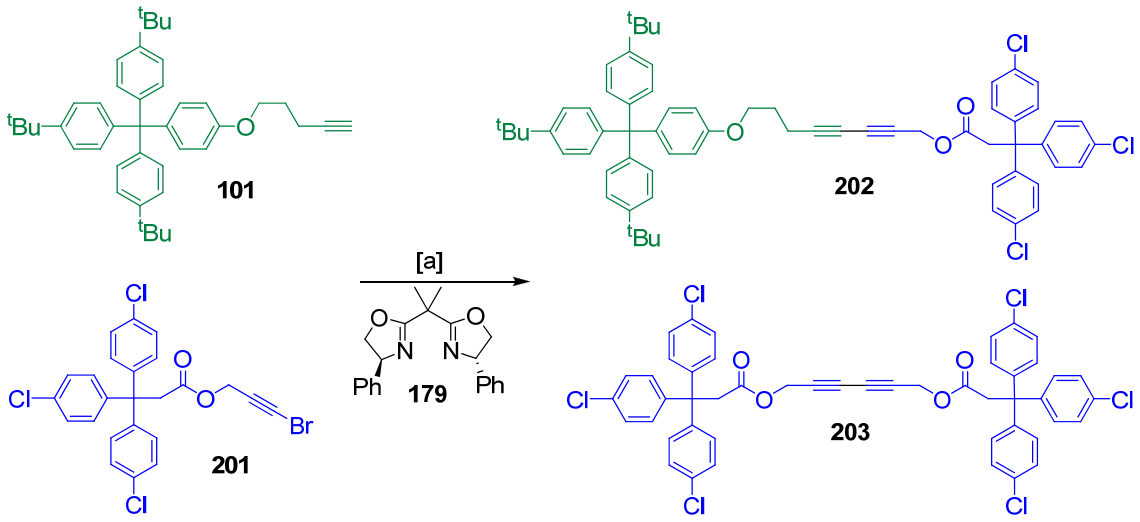


204

Figure 3.3. Homocoupled acetylene **204**.

With a reasonable 70% conversion achieved, initial attempts at optimisation concentrated on the improvement of the ratio of heterocoupled thread, **202**, to homocoupled thread, **203**, from 60:40. In order to achieve this, the amount of Box ligand in the reaction was increased in an attempt to ensure that no background reaction was occurring by providing excess ligand for the copper to ligate with. Doubling the amount of C_2-Box ligand **179** in the reaction did indeed improve the ratio of **202** to **203**, to 85:15 (Table 3.1, entry 2). However, this improvement came with a significant reduction in conversion from bromide **201** to threads **202** and **203**, from 70% to 36%. Lengthening the reaction time to 48 h gave an increase in conversion to 57% (Table 3.1, entry 3), but this poor conversion, along with the precious nature of the C_1-symmetric bis(oxazoline) macrocycle **167**, discouraged us from this line of optimisation.

Table 3.1. Representative Optimisation of Cadiot-Chodkiewicz Reaction with C_2-Symmetric Box Ligand **179**[a]



Entry	Method[a]	Cu(I)	Eq. **179**[b]	Temp. (°C)	Time	Conv. of **201** to **202** + **203** (%)[c]	Ratio **202**:**203**[b]
1	A	CuI	1	RT	20 h	70	60:40
2	A	CuI	2	RT	24 h	36	85:15
3	A	CuI	2	RT	48 h	57	85:15
4	B	CuI	1	RT	24 h	74	74:26
5	B	CuI	-	RT	16 h	23	100:0
6	B	CuI	1	45	24 h	99	75:25
7	B	CuCl	1	45	48 h	100	88:12
8	B	CuCl	1	RT	5 days	100	74:26
9	B	CuCl	-	RT	5 days	34	100:0

[a] Method A: *n*-BuLi (1 eq.), **101** (1 eq.), THF, -78 °C → 0 °C, 15 min; Cu(I) complex (1 eq.), 0 °C→ RT, 15 min; **179** (1 or 2 eq.), **201** (1 eq.), THF, -78 °C → RT. Method B: *n*-BuLi (1 eq.), **101** (1 eq.), THF, -78 °C → 0 °C, 40 min; Cu(I) complex (1 eq.), 0 °C→ RT, 1 h; **179** (1 eq.), **201** (1 eq.), THF, -78 °C → RT. [b] With respect to **201**. [c] Determined by ^{1}H NMR analysis of reaction mixture.

In an attempt to increase both the conversion of the reaction as well as the ratio of heterocoupled to homocoupled thread, the methodology used in the reaction was modified. The times between the addition of each new component in the reaction scheme were lengthened, allowing each stage of the reaction more time to reach completion. Leaving the reaction at 0 °C for 40 min after the addition of *n*-BuLi to acetylene **101** instead of 15 min and stirring this reaction mixture with CuI at room

temperature for 1 hour rather than 15 min before adding Box **179** and bromide **201** resulted in a slight increase in yield (74%, Table 3.1, entry 4) when compared with the original method (70%, Table 3.1, entry 1) and also gave an improvement in the ratio of heterocoupled to homocoupled thread, from 60:40 to 74:26. The conversion of bromide **201** to threads **202** and **203** was significantly better than for the ligand-free control reaction, which only reached a conversion of 23% under similar conditions, although with no evidence of the homocoupled thread **203** (Table 3.1, entry 5). This indicated that the Box ligand **179** promotes the Cadiot-Chodkiewicz coupling of acetylene **101** with bromide **201** compared to the ligand-free background reaction.

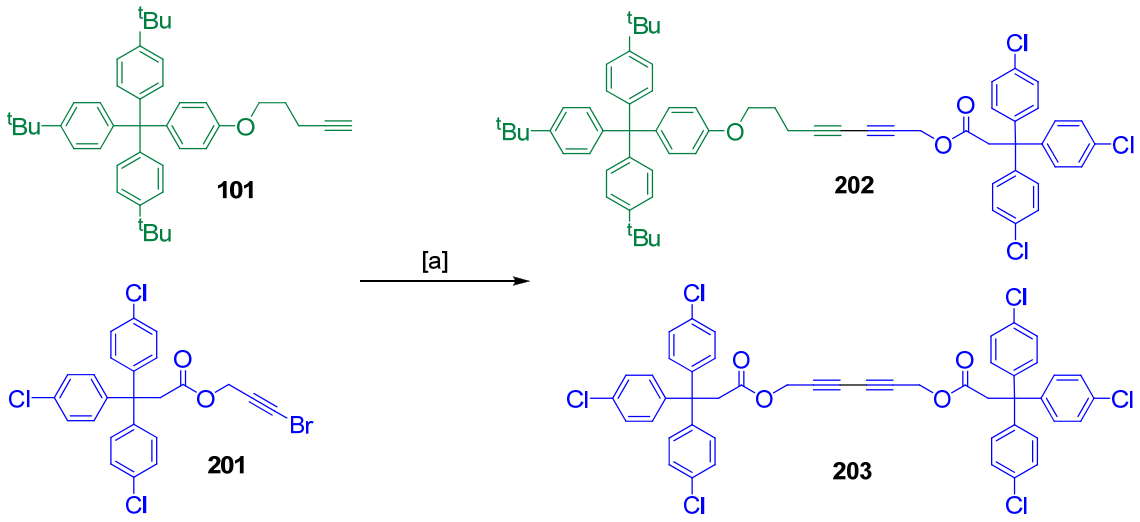
In order to increase the conversion of the reaction above the 75% mark, the temperature of the reaction was increased (Table 3.1, entries 6 and 7). Carrying the reaction out at 45 °C resulted in a conversion of 99% after 24 hours and had very little effect on the ratio of heterocoupled to homocoupled thread (Table 3.1, entry 6). Changing metal source from copper iodide to copper chloride had a significant effect on the ratio of heterocoupled thread, **202**, to homocoupled thread, **203**, increasing it to 88:12 under these reaction conditions, whilst giving 100% conversion from bromide **201** to thread (Table 3.1, entry 7). Although the higher temperature gave complete conversion it may have a detrimental effect on the asymmetric approach of the stoppers to the sterically different faces of the macrocycle, possibly providing enough energy for the barrier of steric hindrance to be overcome and hence destroying the asymmetric nature of the rotaxane-forming methodology. Thus, further optimisation was carried out at room temperature.

Optimisation of the room temperature Cadiot-Chodkiewicz reaction was achieved by increasing the reaction time. Complete conversion of bromide **201** to threads **202** and **203** was obtained after 5 days (Table 3.1, entry 8). The ratio of heterocoupled thread **202** to homocoupled thread **203** was 74:26. Once again, the Box-mediated reaction proved more effective than the ligand-free reaction, which could only reach a conversion of 34% after 5 days, although again with no evidence of homocoupled thread **203** (Table 3.1, entry 9).

Trial of Optimised Conditions

Encouraged by the optimisation of the Cadiot-Chodkiewicz reaction for C_2-Box ligand **179**, the reaction was attempted with both model C_1-Box ligand **181** and macrocycle **167** (Table 3.2, entries 1 and 2). Surprisingly, neither of the reactions gave any indication of threads **202** or **203**. As the control reaction run in the absence of any ligand (Table 3.2, entry 3) gives a conversion to heterocoupled thread **202** of 34%, it would appear that the non-macrocycle C_1-Box ligand **181** and C_1-macrocycle **167** are *inhibiting* the reaction. This is in direct contrast with C_2-Box ligand **179** which promotes the reaction to complete conversion (Table 3.2, entry 4).

Table 3.2. Trial of Optimised Conditions for Cadiot-Chodkiewicz Reaction[a]



Entry	Box	Conv. of **201** to **202** + **203** (%)[b]	Ratio **202**:**203**[b]
1	**181**	0	-
2	**167**	0	-
3	-	34	100:0
4	**179**	100	0.74:0.26
5	**180**	22	100:0

[a] Reaction conditions: *n*-BuLi (1 eq.), **101** (1 eq.), THF, -78 °C → 0 °C, 40 min; Cu(I) complex (1 eq.), 0 °C→ RT, 1 h; Box (1 eq.), **201** (1 eq.), THF, -78 °C → RT, 5 days. [b] Determined by ^{1}H NMR analysis of reaction mixture.

There are two possibilities for this outcome: either the benzyl (*vs.* Ph) group is inhibiting the reaction; or the steric hindrance of having both groups on the same face of the ligand is too great for the reaction to occur. To ascertain the cause, the reaction was

carried out with commercially available C_2-symmetric *dibenzyl* Box ligand **180** (Table 3.2, entry 5). The conversion of bromide **201** to thread **202** was significantly lower for the dibenzyl Box ligand **180** than for the diphenyl Box compound **179** (22% *vs.* 100%) and was also lower than for the ligand-free reaction (22% *vs.* 34%). This would imply that the dibenzyl Box ligand **180** inhibits the Cadiot-Chodkiewicz reaction. It would appear, therefore, that the presence of a benzyl group in conjunction with the C_1 nature of the ligand, with its steric crowding of one face of the compound, completely prevents the Cadiot-Chodkiewicz reaction from occurring in the presence of Box ligand **181** and macrocycle **167**.

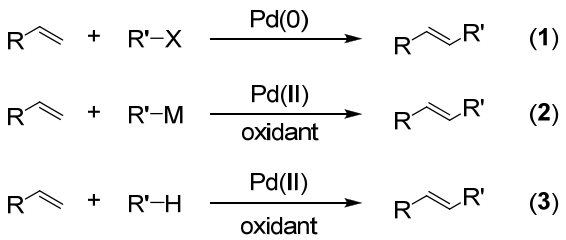
3.3.5. Conclusion

The Cadiot-Chodkiewicz heterocoupling of acetylenes was investigated as a possibility for use in the asymmetric synthesis of mechanically planar chiral rotaxanes. Although the reaction was found to be compatible with the use of bis(oxazoline) ligands, being optimised to give complete conversion from bromide **201** to threads **202** and **203**, it was found to be sensitive to the nature of the bis(oxazoline) ligand, showing no reaction with C_1-model Box ligand **181** or macrocycle **167**.

3.4. Oxidative Heck Reaction

3.4.1. Introduction

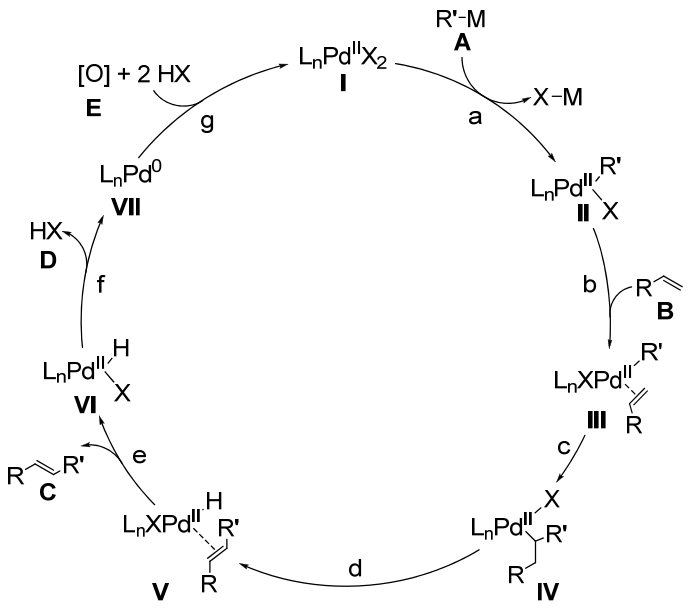
The oxidative version of the Mizoroki-Heck reaction, coupling of an alkene with an organohalide,[272, 273] has proven a popular alternative to the classic reaction (eq. 1, Scheme 3.10).[274-276] The use of palladium(II) catalysts with organometallic compounds is the most prevalent type of oxidative Heck reactions (eq. 2, Scheme 3.10), although direct C-H activation of arenes,[277] acetylenes,[278-280] indoles,[281] pyrroles[282] and thiazoles[283] (eq. 3, Scheme 3.10) and the use of other transition metals such as ruthenium[284] are also known.



Scheme 3.10. Mizoroki-Heck and oxidative Heck reactions.

The first oxidative Heck reaction was reported in 1968 coupling organomercuric compounds and alkenes with palladium(II) catalysts.[285] Other compounds used in the oxidative Heck reaction include organophosphonic acids,[286] arylsulfonyl hydrazines,[287] organostannanes[288] and organosilanols.[289] Boronic acids are the more common organometallic species used for the oxidative Heck reaction as they are less toxic than most of the other compounds, stable to air and commercially available.[290] They have been used in the synthesis of natural products,[291-293] in tandem reactions[294] and in asymmetric synthesis.[243, 244, 295]

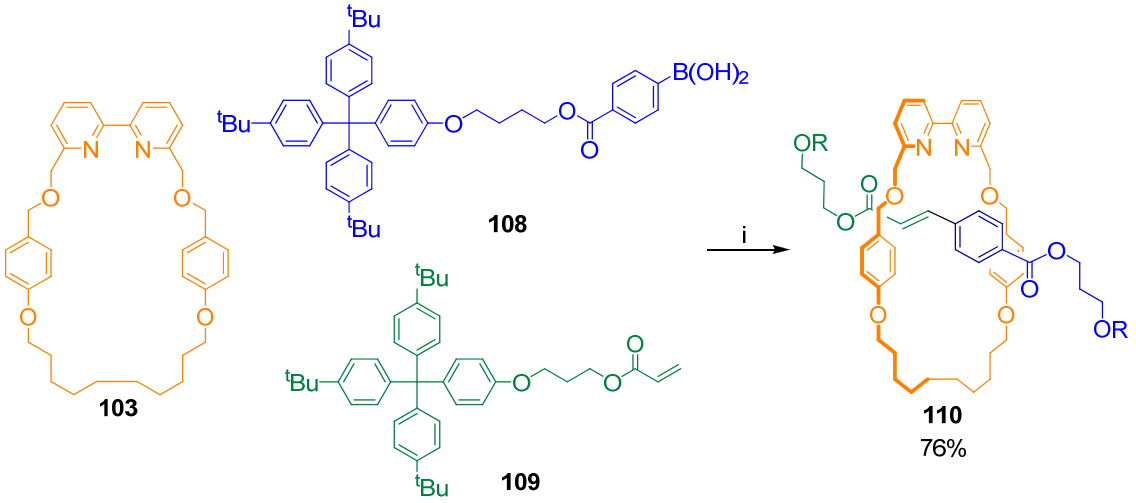
The proposed reaction mechanism for the oxidative Heck reaction is outlined in Scheme 3.11.[296] Transmetalation of the palladium(II) catalyst **I** with the organometallic reagent **A** gives organopalladium(II) species **II** (a, Scheme 3.11). Alkene coordination followed by migratory insertion produces compound **IV** (b and c, Scheme 3.11) which can undergo β-hydride elimination to palladium-hydride **V** (d, Scheme 3.11). Alkene dissociation then gives the coupling product **C** and palladium-hydride **VI** (e, Scheme 3.11) which regenerates palladium(II) species **I** by successive reductive elimination and oxidative addition with the oxidant additive **E** (f and g, Scheme 3.11).



Scheme 3.11. Mechanism of the oxidative Heck coupling reaction. a) Transmetallation. b) Alkene co-ordination. c) Migratory insertion. d) β-Hydride elimination. e) Dissociation. f) Reductive elimination. g) Oxidation. [296]

Oxidative Heck in Rotaxane Synthesis

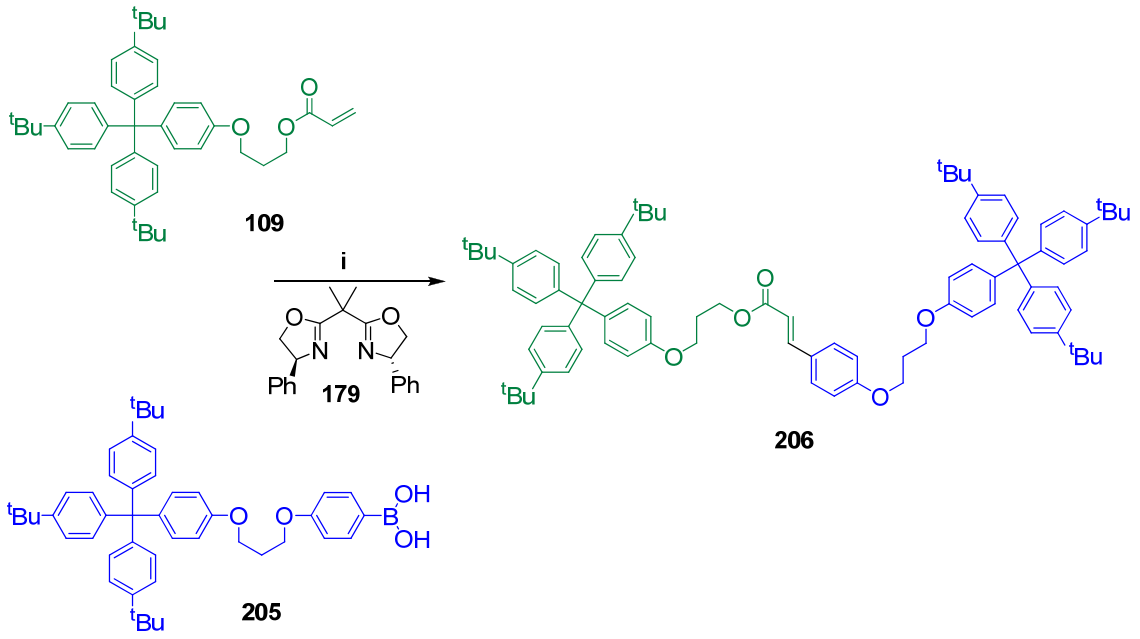
The oxidative Heck coupling of boronic acids and alkenes was used by Leigh *et al.* in the active metal template synthesis of rotaxanes (Scheme 3.12).[153] The reaction was catalytic, with only 1 - 10 mol% of the palladium catalyst required, and used bipyridine macrocycle **103** as ligand. A range of alkene and boronic acid stopper groups were trialled, each producing an non-symmetric thread, with the best giving a yield of rotaxane of 76% (Scheme 3.12). This promising rotaxane formation yield using the oxidative Heck reaction was the starting point for the investigation of the reaction in the asymmetric active template synthesis of rotaxanes.



Scheme 3.12. Oxidative Heck active metal synthesis of rotaxane **110**. Reagents and conditions: (i) **103**, $Pd(OAc)_2$ (10 mol %), **108**, **109**, benzoquinone, 1:1 $CHCl_3/CH_2Cl_2$, O_2, RT, 72 h.[153]

3.4.2. Suitability of Box Ligands in the Oxidative Heck Reaction

Although bis(oxazoline)s are known in the literature as ligands for oxidative Heck reactions these are limited to a couple of examples[243, 244] and no studies of their reactivity in these reactions has been reported. Therefore, a trial reaction using the stopper groups and conditions derived by Leigh *et al.*[153] for the active template oxidative Heck formation of rotaxanes was carried out (Scheme 3.13). A conversion from alkene stopper **109** to thread **206** of 35% was obtained, compared with the 73% yield achieved by Leigh *et al.* using a bipyridine macrocycle.[153] Despite the low conversion, this indicated that Box ligands can be used successfully in the oxidative Heck reaction.

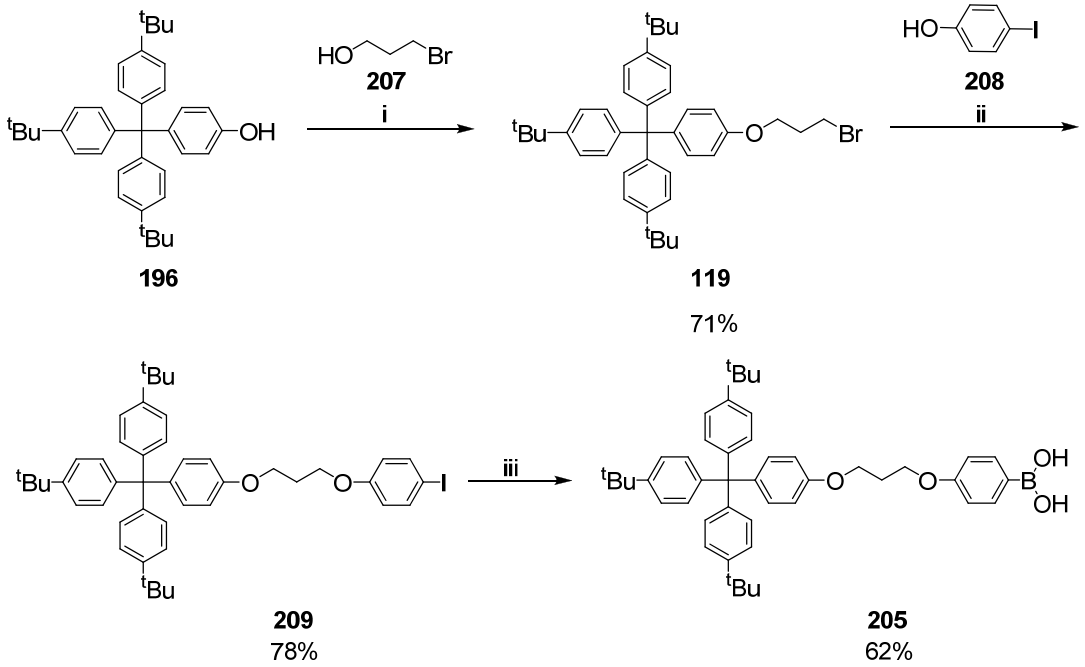


Scheme 3.13. Oxidative Heck trial with Box ligand **179**. Reagents and conditions: (i) **179**, $Pd(OAc)_2$ (20 mol%), benzoquinone, O_2, 1:1 DCM:$CHCl_3$, RT, 92 h, conversion 35%.

3.4.3. Non-symmetric Stoppers for the Oxidative Heck Reaction

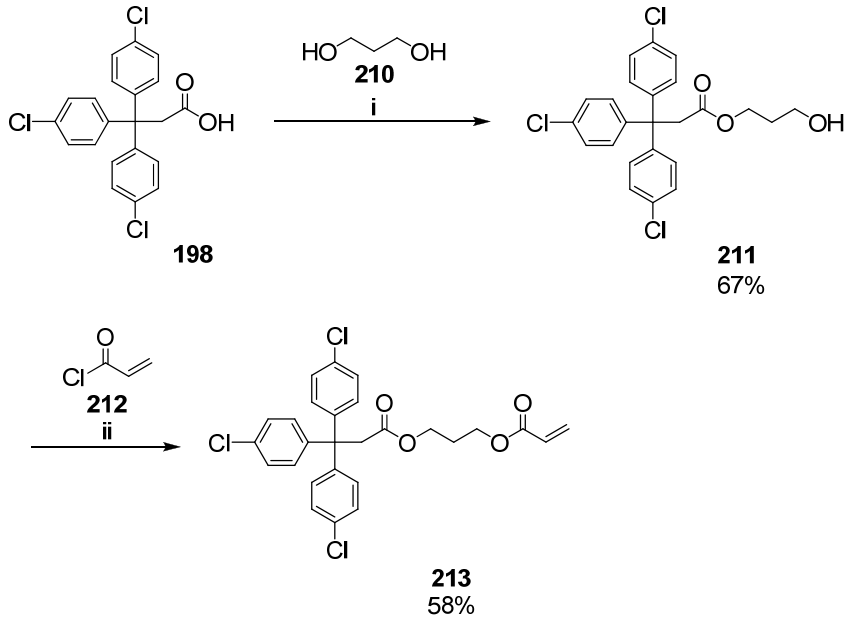
As with the Cadiot-Chodkiewicz reaction, the stoppers utilised by Leigh *et al.* in the oxidative Heck formation of rotaxanes, although producing a non-symmetric thread, are structurally very similar. Once again the asymmetry of the thread was increased by using half-threads with significantly different stopper groups.

Boronic acid **205** is the same used in the trial oxidative Heck reaction for Box ligands (Scheme 3.13) and has been utilised by Leigh *et al.* in their rotaxane synthesis.[153] It was synthesised following literature procedures (Scheme 3.14).[153] DIAD-promoted coupling of 4-[tris-(*p*-*tert*-butyl-phenyl)-methyl]phenol **196** and 3-bromopropan-1-ol **207** with addition of triphenylphosphine gave bromide **119** in a 71% yield. Treatment of bromide **119** with 4-iodophenol **208** and potassium carbonate produced iodide **209** in a 78% yield. Boronic acid **205** was achieved through reaction of iodide **209** with *n*-butyl lithium followed by treatment with trimethyl borate in a 62% yield.



Scheme 3.14. Synthesis of boronic acid stopper **205**. Reagents and conditions: (i) **207** , DIAD, PPh_3, argon, THF, RT, 67 h; (ii) **208**, K_2CO_3, butanone, 80 °C, 42 h; (iii) *n*-BuLi, $B(OMe)_3$, THF, RT, 39 h.

Synthesis of the alkene stopper for the oxidative Heck reaction, **213**, starts with the EDCI-promoted coupling of 3,3,3-tris(4-chlorophenyl)propanoic acid **198** with propane-1,3-diol **210** to provide alcohol **211** in a 67% yield (Scheme 3.15). Treatment of alcohol **211** with acrylolyl chloride **212**, triethylamine and DMAP results in the formation of alkene stopper **213** in a 58% yield.



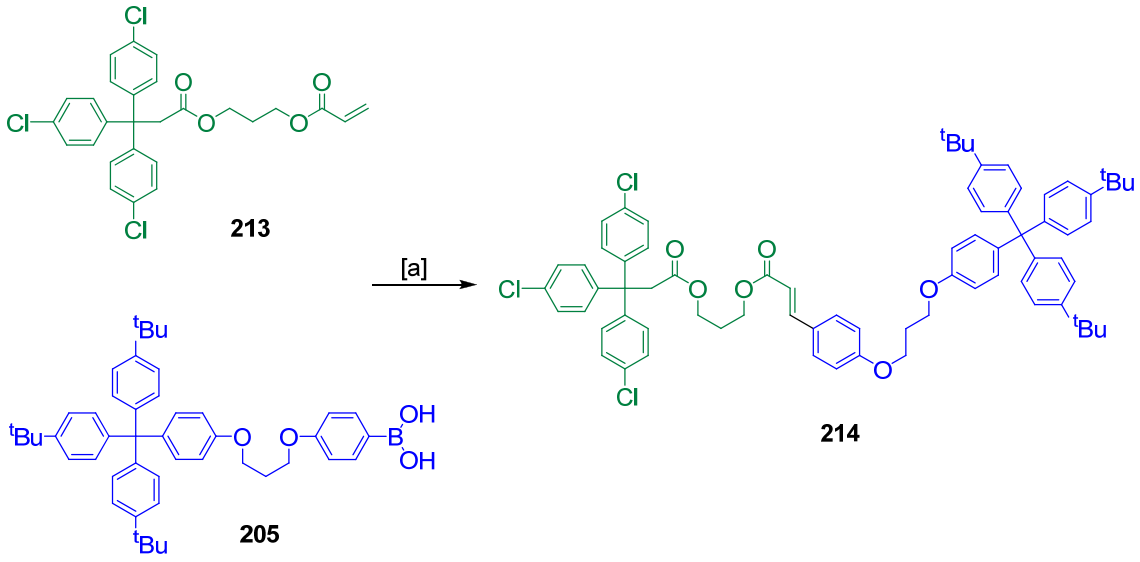
Scheme 3.15. Synthesis of alkene stopper **213**. Reagents and conditions: (i) **210**, EDCI, DMAP, DCM, RT, 22 h; (ii) **212**, Et_3N, DMAP, DCM, RT, 2 h.

3.4.4. Oxidative Heck Reaction Trials

Optimisation of Reaction Conditions

With the new stoppers for the oxidative Heck reaction in place, optimisation of the reaction for bis(oxazoline) ligands could begin (Table 3.3).

Table 3.3. Representative Optimisation of Oxidative Heck Reaction[a]



Entry	Box	Eq. **205**[b]	Oxidant	Solvent[c]	Time (h)	Conv. of **213** to **214** (%)[d]
1	-	3	BQ/O_2	$DMF:CHCl_3$	48	24
2	-	3.5	BQ	$DMF:CHCl_3$	48	53
3	-	3	BQ	$DCM:CHCl_3$	48	34
4	**179**	3	BQ	$DMF:CHCl_3$	48	100
5	**181**	3	BQ	$DMF:CHCl_3$	49	59
6	**181**	4	BQ	$DMF:CHCl_3$	50	47
7	**181**	3	BQ	$DMF:CHCl_3$	120	43
8	**181**	3	BQ/O_2	$DMF:CHCl_3$	48	100

[a] General reaction conditions: $Pd(OAc)_2$ (20 mol%) with respect to **213**, Box ligand (1 eq.), DMF or DCM, RT, 2.5 h; **213** (1 eq.), **205** (3 or 4 eq.), benzoquinone (1 eq.), $CHCl_3$, N_2 or O_2, 25 °C. [b] With respect to **213**. [c] 1:1 mixture of solvents. [d] Determined by ^1H NMR analysis of reaction mixture. BQ = benzoquinone.

In an attempt to increase the conversion of starting materials to thread from the 35% attained in the trial reaction (Scheme 3.13), the equivalents of boronic acid **205** with

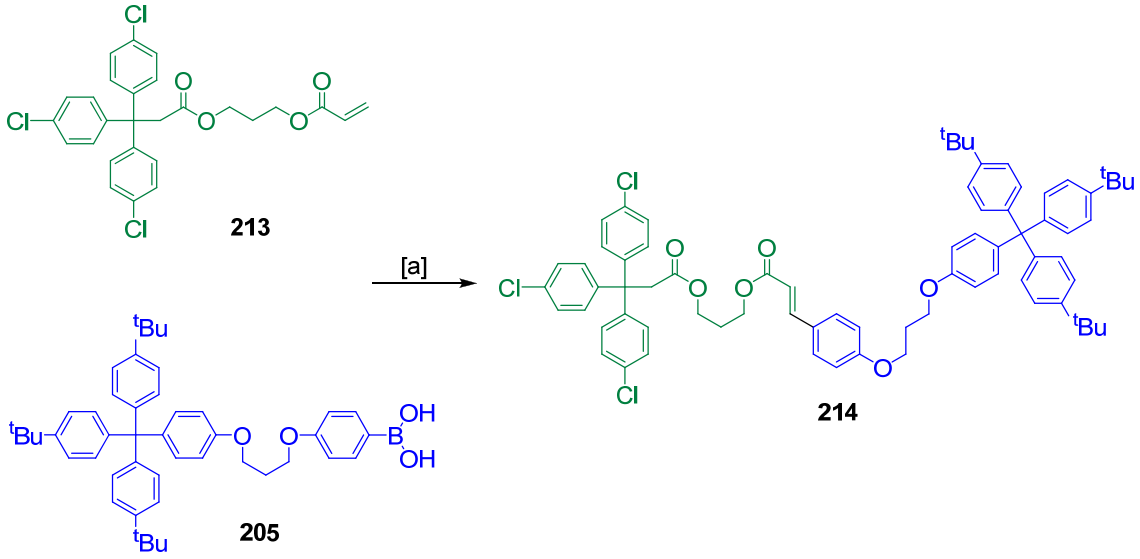
respect to alkene **213** were increased from 2 to 3. Investigation into both the solvent and oxidant used in the reaction was carried out in the absence of Box ligand (Table 3.3, entries 1-3). Changing oxidant from benzoquinone and oxygen to benzoquinone alone more than doubled the conversion of alkene **213** to thread **214** (Table 3.3, entries 1 and 2) and moving from 1:1 DCM-chloroform to 1:1 DMF-chloroform (as the components of the reaction do not dissolve in DMF alone) increased the conversion from 34% to 53% (Table 3.3, entries 2 and 3). Once the reaction was carried out in the presence of C_2-symmetric Box ligand **179**, complete conversion from alkene **213** to thread **214** was achieved (Table 3.3, entry 4).

Having achieved complete conversion from stopper to thread in the oxidative Heck reaction using C_2-Box ligand **179**, the reaction was carried out with C_1-Box macrocycle substitute **181**. Unfortunately, a conversion of alkene **213** to thread **214** of only 59% was achieved (Table 3.3, entry 5). Attempts at improving the conversion by either increasing the equivalents of boronic acid from three to four (Table 3.3, entry 6) or increasing the reaction time from 48 to 120 hours (Table 3.3, entry 7) had a detrimental effect, lowering the conversion to 47% and 43% respectively. However, the addition of oxygen to the reaction as an extra oxidant achieved complete conversion of stopper **213** to thread **214** with C_1-Box **181** as ligand (Table 3.3, entry 8).

Rotaxane Trials

Encouraged by the complete conversion of alkene **213** to thread **214** by the non-macrocyclic C_1-Box ligand **181**, synthesis of rotaxane **215** was attempted. Unfortunately, a conversion to non-interlocked thread **214** of only 21% was achieved (Table 3.4, entry 1), similar to that of the ligand-free reaction (Table 3.4, entry 2). It is also in the region of what would be expected if the palladium catalyst was not turning over in the reaction (20%). Therefore, the reaction was repeated with stochiometric amounts of $Pd(OAc)_2$ in order to determine if the macrocycle was sequestering the palladium and preventing turn over (Table 3.4, entry 3). The conversion of alkene **213** to non-interlocked thread **214** achieved under these conditions was only 50%, similar to the conversion obtained from the ligand-free stochiometric control reaction (Table 3.4, entry 4, 47%). This similarity, when coupled with the lack of rotaxane **215** in the reaction, implies that the Box macrocycle **167** is not bound to the palladium throughout the reaction and only the background reaction is being observed.

Table 3.4. Trials of Oxidative Heck Reaction for Rotaxane Formation[a]



Entry	Box	$Pd(OAc)_2$ (mol%)[b]	Solvent[c]	Conv. of **213** to **214** (%)[d]	Rotaxane **215** (%)[e]
1	**167**	20	$DMF:CHCl_3$	21	N/A
2	-	20	$DMF:CHCl_3$	24	N/A
3	**167**	100	$DMF:CHCl_3$	50	0
4	-	100	$DMF:CHCl_3$	47	N/A
5	-	20	$CHCl_3$	31	N/A
6	**181**	20	$CHCl_3$	20	N/A
7	**167**	20	$CHCl_3$	5	0

[a] General reaction conditions: $Pd(OAc)_2$, Box ligand (1 eq.), DMF or $CHCl_3$, RT, 2.5 h; **213** (1 eq.), **205** (3 eq.), benzoquinone (1 eq.), $CHCl_3$, N_2 or O_2, 25 °C, 48 h. [b] With respect to **213**. [c] 1:1 mixture of solvents. [d] Determined by ^1H NMR analysis of reaction mixture. [e]Determined by mass spectrometry of reaction mixture.

Suspecting competition between the macrocycle **167** and DMF in ligating to the palladium catalyst, the reaction was run in chloroform alone as this has a lower binding affinity to transition metals than DMF.[297] A ligand-free control reaction indicated that chloroform was a suitable solvent for the oxidative Heck reaction between alkene **213** and boronic acid **205**, achieving a better conversion than the ligand-free control in $DMF:CHCl_3$, though still quite low at 31% (Table 3.4, entry 5). When the reaction was carried out with non-macrocyclic C_1-Box ligand **181** and macrocycle **167** (Table 3.4, entries 6 and 7) the conversions were lower than those obtained in the control reaction; 20% and 5% respectively. It is apparent from these results that both the non-

macrocyclic Box ligand **181** and macrocycle **167** are ligated to the metal catalyst throughout the reaction and are slowing down the reaction compared to the ligand-free control. This supports our conjecture that DMF is competing with the Box macrocycle **167** in ligating with the palladium. It would appear from these results that there is a series in binding affinity to palladium between the solvent and Box ligands which runs as follows: non-macrocyclic C_2-Box **179** ~ non-macrocyclic C_1-Box **181** > DMF > Box macrocycle **167**.

Although a reaction where the Box macrocycle **167** was bound to the palladium catalyst throughout was achieved, the macrocycle slowed down the reaction so much that it appeared unlikely that optimisation to obtain complete conversion of alkene **213** to non-interlocked thread **214** and rotaxane **215** would be possible. It appears that, despite the ligand-free control reactions, which show that DMF slows down the rate of reaction compared to chloroform alone (Table 3.4, entries 2 and 5), in the presence of a bound Box ligand, *e.g.* C_1-Box **167**, DMF appears to help accelerate the reaction (100% conversion *vs.* 20% conversion, Table 3.3, entry 8 and Table 3.4, entry 6). It would appear that the Box-mediated oxidative Heck reaction requires the presence of polar solvents to achieve complete conversion in a relatively short time-scale. Unfortunately, most of the polar solvents used for the reaction, *e.g.* DMSO, methanol and THF, have similar binding affinities for transition metals as DMF and would therefore not be suitable for the rotaxane-forming reaction.[297]

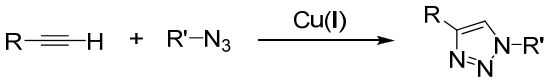
3.4.5. Conclusion

The oxidative Heck reaction of an alkene and boronic acid was investigated as a possibility for use in the asymmetric synthesis of mechanically planar chiral rotaxanes. The reaction was promising with bis(oxazoline) macrocycle ligands **179** and **181**, indicating that Box ligands could be used in the reaction. However, macrocycle **167** failed to ligate to the palladium complex, being in competition with the DMF in the reaction. Attempts to circumvent this competition were successful, but resulted in poor conversion from alkene **213** to non-interlocked thread **214**. The low binding affinity of macrocycle **167** for the palladium complex compared to that for C_1-symmetric Box ligand **181** may be due to the increased steric bulk of the macrocycle around the Box moiety or to possible changes in geometry around the Box moiety due to the strain of being within a macrocycle.

3.5. CuAAC 'Click' Reaction

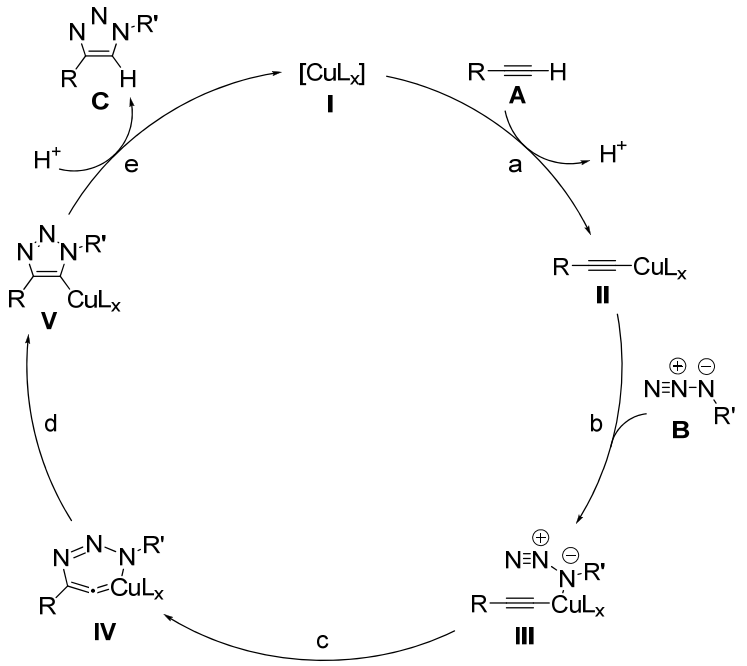
3.5.1. Introduction

'Click' chemistry was defined by Sharpless, Finn and Kolb as an approach to chemistry where modular building blocks are joined together with high yields in a stereoselective and simple reaction which has a wide scope and non-toxic byproducts.[298] The most common reaction used in the 'click' methodology is the Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction, first reported in 2002 by Sharpless[299] and Meldal[300] independently (Scheme 3.6). There are several reviews on the CuAAC 'click' reaction and over a thousand research articles have been published on the subject.[301-305] A range of copper(I) catalysts and a variety of solvents, including DCM, THF, DMF and DMSO, can be used in the reaction.[302]

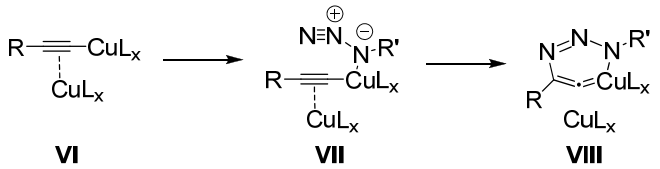


Scheme 3.16. Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction.

Fokin and co-workers have proposed a reaction mechanism for the CuAAC 'click' reaction based on DFT analysis (Scheme 3.17).[303, 306-308] Step one is the formation of copper acetylide **II** from copper(I) catalyst **I** and alkyne **A**, followed by the coordination of azide **B** to give complex **III** (a and b, Scheme 3.17). Formation of 6-membered copper metallacycle **IV** (c, Scheme 3.17) is quickly followed by synthesis of copper triazolide **V** (d, Scheme 3.17). Dissociation of the triazole **C** (e, Scheme 3.17) regenerates copper(I) catalyst **I**. A lower energy pathway for the reaction was discovered by Fokin *et al.* where copper(I) acetylide **VI** interacts with a second copper atom to provide a more stable structure, **VII** (Scheme 3.18).[307] This leads into intermediate **VIII**, where the second copper reduces the energy of the structure. The reaction has also been found to be more complex than expected, with off-cycle pathways having an effect on the reaction.[303]



Scheme 3.17. Proposed reaction mechanism of the CuAAC 'click' reaction. a) Ligand exchange. b) Ligand exchange. c) Cyclisation. d) Rearrangment. e) Protonation/dissociation.[303]



Scheme 3.18. Proposed lower energy bimetallic pathway for the CuAAC 'click' reaction.[307]

CuAAC 'Click' Reaction in Supramolecular Chemistry

The CuAAC 'click' reaction is widely used in the field of supramolecular chemistry; recently in the synthesis of liquid crystal materials,[309] insulated wires,[310] macrocycles,[311, 312] 3-point star molecules[313] and molecular knots.[314] Sauvage and Stoddart pioneered the use of the CuAAC 'click' reaction in the template synthesis of rotaxanes; Sauvage utilising a copper template,[315] Stoddart a π-acceptor/π-donor template (Figure 3.4).[24] There are numerous examples of passive template synthesis of rotaxanes and catenanes with the CuAAC 'click' reaction in the literature.[51, 60, 64, 65, 73, 119, 316-335]

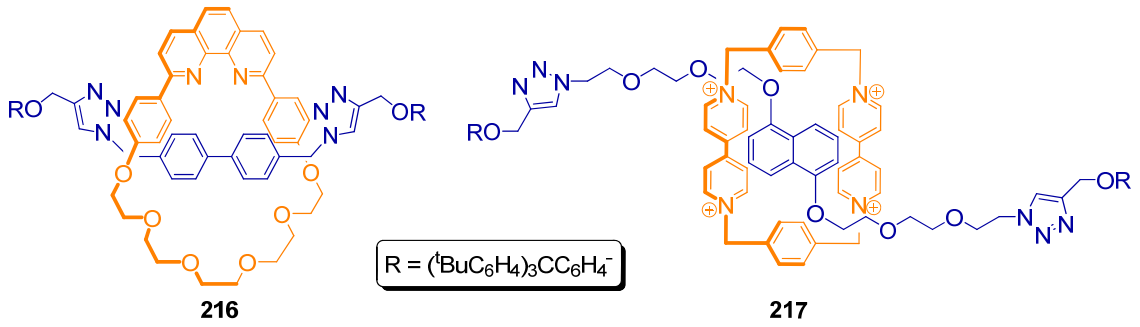
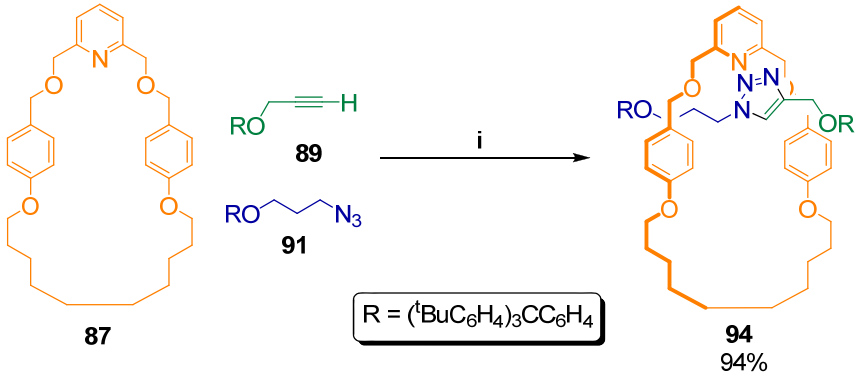


Figure 3.4. Template synthesis of rotaxanes with the CuAAC 'click' reaction. Copper template (**216**)[315] and π-acceptor/π-donor template (**217**).[24]

Leigh and co-workers pioneered the active template synthesis of rotaxanes, where the metal acts as both template and catalyst for the rotaxane-forming reaction, with the CuAAC 'click' reaction.[145] Rotaxane **94** was synthesised from acetylene **89** and azide **91** with pyridine macrocycle **87** as ligand in a 94% yield (Scheme 3.19). Leigh has also investigated other pyridine-based macrocycles in the CuAAC 'click' active template synthesis of rotaxanes[43] and Goldup has investigated the effect of the size of the macrocycle cavity on the reaction.[336] Leigh *et al.* have also extended the use of the CuAAC 'click' reaction into the active template synthesis of [3]rotaxanes,[337] catenanes[270] and trefoil knots.[314]

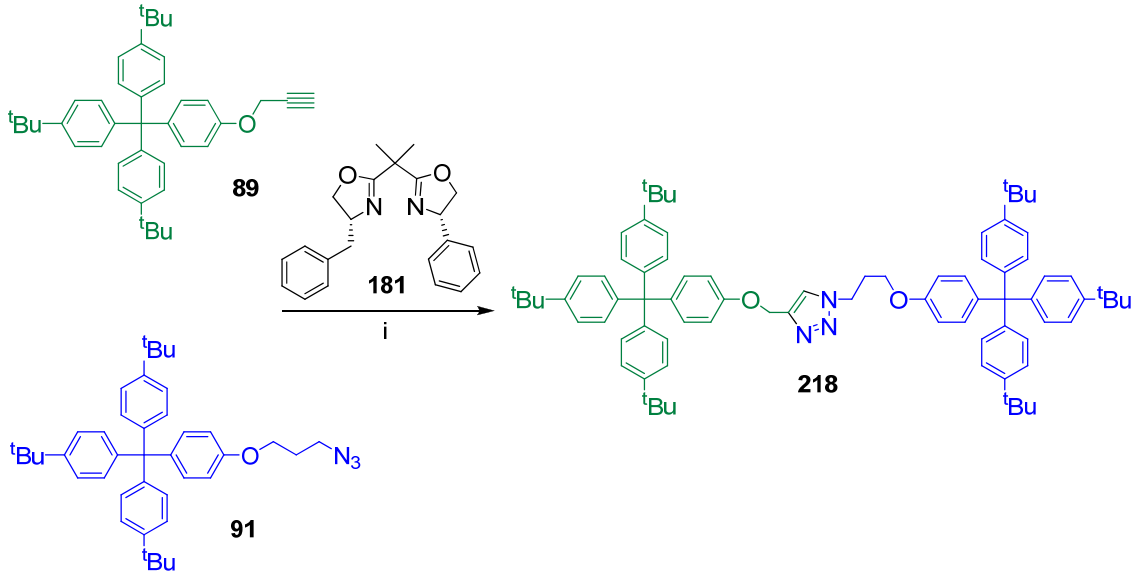


Scheme 3.19. CuAAC 'click' active template synthesis of rotaxane **94**. Reagents and conditions: (i) **97** (1 eq.), **89** (5 eq.), **91** (5 eq.), $Cu(CH_3CN)_4PF_6$ (1 eq.), DCM, RT, 24 h, reflux, 18 h.[145]

The extensive use of the CuAAC 'click' reaction in the synthesis of rotaxanes and catenanes is an excellent foundation for its trial in the asymmetric synthesis of mechanically planar chiral rotaxanes.

3.5.2. Suitability of Box Ligands in the CuAAC 'Click' Reaction

In order to determine if bis(oxazoline) compounds would be suitable ligands for the CuAAC 'click' reaction, a trial reaction using some of the stoppers developed by Leigh *et al.* for the rotaxane-forming CuAAC 'click' reaction was performed (Scheme 3.20).[43, 145] The conditions used were those developed by Goldup *et al.* for the formation of a bipyridine rotaxane, carrying the reaction out in dichloromethane at 80 °C in a sealed vessel.[336] A reasonable conversion of acetylene **89** to thread **218** of 60% was achieved, indicating that bis(oxazoline) compounds are suitable ligands for the reaction.



Scheme 3.20. Trial of the CuAAC 'click' reaction with Box ligand **181**. Reagents and conditions: (i) $CuPF_6{\cdot}(CH_3CN)_4$, DCM, 80 °C, 72 h, conversion 60%.

3.5.3. CuAAC 'Click' Reaction Trials

Stoppers

Once again, in order to increase the asymmetry of the thread, and therefore the rotaxane, produced in the CuAAC 'click' reaction, half-threads with vastly different stopper groups were utilised. Azide **91** used in the trial reaction was retained and acetylene **200**, previously synthesised on the route towards Cadiot-Chodkiewicz bromide stopper **201**, was used instead of acetylene **89** (Figure 3.5). The coupling of these two half-threads will produce a suitably non-symmetric thread for our purposes.

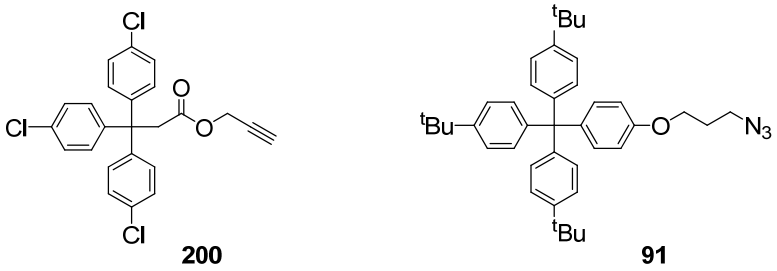
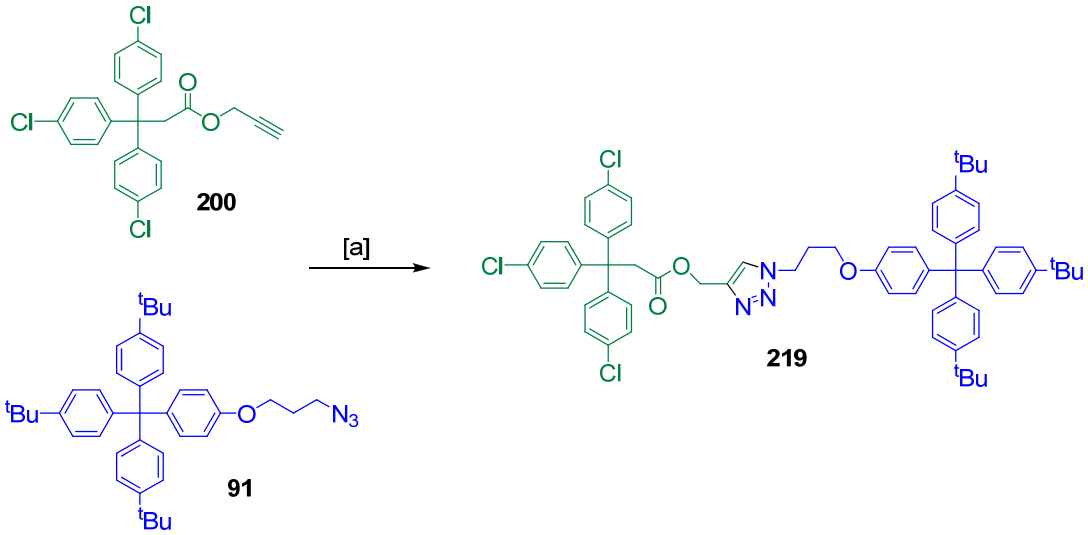


Figure 3.5. Stoppers for the CuAAC 'click' reaction: alkene **200** and azide **91**.

Initial Trials

Following the successful trial of C_1-symmetric macrocycle substitute **181** with stoppers **91** and **89** (Scheme 3.20), the initial reaction of acetylene **200** with azide **91** was carried out using the same reaction conditions (Table 3.5).

Table 3.5. Initial Trials of CuAAC 'Click' Reaction[a]



Entry	Box	Time	Conv. of **200** to **219** (%)[b]	Rotaxane **220** (%)[b]
1	**181**	68 h	100	-
2	**167**	72 h	100	0

[a] Reaction conditions: $CuPF_6(CH_3CN)_4$ (1 eq.), Box ligand (1 eq.), DCM, RT, 1 h; **200** (1 eq.), **91** (1 eq.), DCM, 80 °C. [b] Determined by ^{1}H NMR analysis of reaction mixture.

To our surprise, these reaction conditions resulted in complete conversion of acetylene **200** to thread **219** (Table 3.5, entry 1) in comparison to the 60% achieved with acetylene **89** (Scheme 3.20). Buoyed by this unexpectedly good result, the reaction with macrocycle **167** was attempted using the same conditions. Once again, complete conversion from acetylene **200** to products was achieved (Table 3.5, entry 2). However,

there was no evidence of rotaxane **220** in the ^{1}H NMR spectrum, which showed no shift in the peaks from those of non-interlocked thread **219** as would be expected in a rotaxane. We speculated that the macrocycle may no longer be bound to the copper species at the high temperatures used in the reaction (80 ^oC). It was therefore decided to optimise the CuAAC reaction at room temperature.

Optimisation of Reaction Conditions

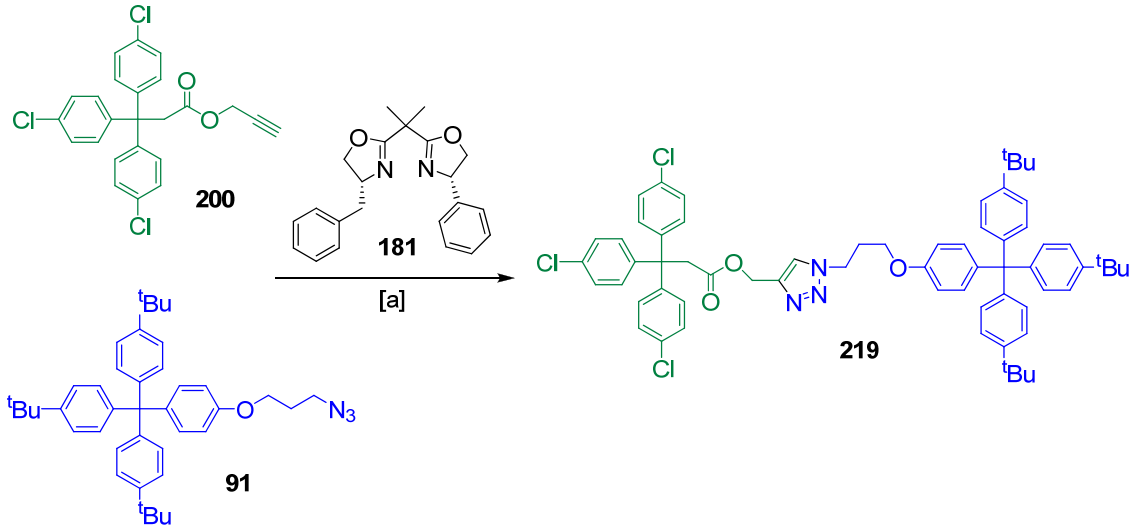
The optimisation of the CuAAC 'click' reaction at room temperature started with a ligand-free control reaction (Table 3.6, entry 1). It indicated that the reaction could be carried out at 25 °C, and was complete within the same time frame as the 80 °C reaction. The reaction was then carried out with C_1-symmetric Box ligand **181** (Table 3.6, entry 2). Monitoring the reaction, it was found to be much slower than the ligand-free control, reaching only 40% conversion with respect to acetylene **200** after 7 days of reaction. Although a poor result in terms of the conversion of the reaction, this result indicated that the Box ligand was bound to the copper throughout the reaction as any background reaction would have resulted in complete conversion to thread **219** in a much shorter period of time. This result therefore gave us hope that rotaxane was achievable at room temperature.

Unfortunately, the initial result proved to be irreproducible. It was discovered that the problem lay in the concentration of the reaction. All the original reactions were run in round-bottomed flasks with Suba-Seal septa. As the reaction solvent was dichloromethane, which can be absorbed by Suba-Seal septa, we were observing a variable concentration in the reactions, both throughout the reaction time scale and also between the different reactions. This was having more of an affect than originally thought, resulting in widely varying results. By changing from round-bottom flasks with Suba-Seal septa to sealed sample vials, concentration could be controlled throughout the reaction, giving reproducible results.

The initial investigation into the effect of concentration into the CuAAC 'click' reaction was carried out in a relatively dilute solution of 0.01 M with respect to Box **181** (Table 3.6, entry 3). Surprisingly, this gave very little conversion, even after 7 days. By increasing the concentration to 0.06 M, a 40% conversion after 4 days was achieved (Table 3.6, entry 4). Complete conversion of acetylene **200** to thread **219** was achieved

in only 48 hours through further concentration, to 0.40 M, and with the use of additional azide **91**, as this was found to be a limiting factor (Table 3.6, entry 5).

Table 3.6. Representative Optimisation of the CuAAC 'Click' Reaction with C_1-Box Ligand **181**[a]



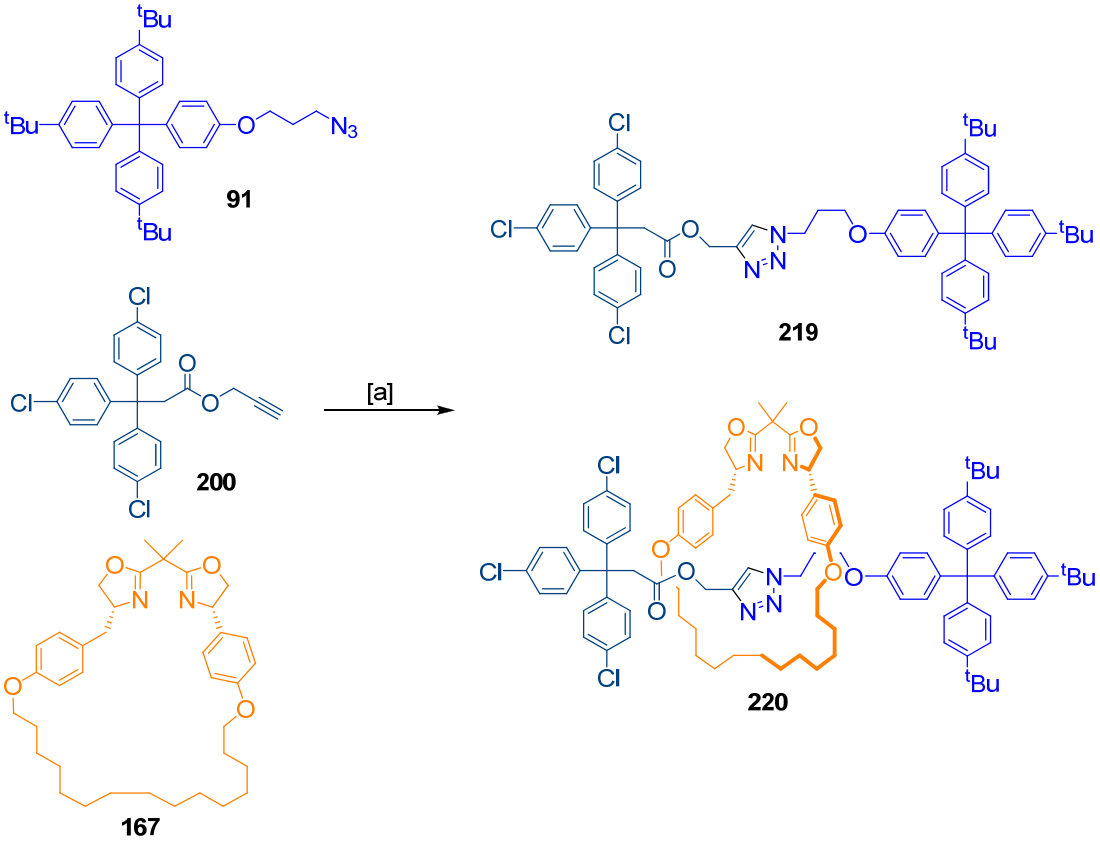
Entry	Box	Conc. (M)[b]	Time	Conv. of **200** to **219** (%)[c]
1	-	0.01[d]	74 h	100
2	**181**	0.01[d]	7 days	40
3	**181**	0.01	7 days	< 10
4	**181**	0.06	4 days	40
5[e]	**181**	0.40	48 h	100

[a] Reaction conditions: $CuPF_6{\cdot}(CH_3CN)_4$ (1 eq.), **181** (1 eq.), DCM, RT, 2.5 h; **200** (1 eq.), **91** (1 eq.), DCM, 25 °C. [b] With respect to **181**. [c] Determined by ^{1}H NMR analysis of reaction mixture. [d]Variable concentration due to solvent evaporation. [e] With 1.5 eq. of **91**.

Rotaxane Trials

With the optimised reaction conditions for the CuAAC 'click' reaction with C_1-symmetric Box ligand **181** in hand, attention turned to the synthesis of rotaxane **220**. To our delight, complete conversion from acetylene **200** to non-interlocked thread **219**, was achieved (Table 3.7, entry 1). However, rotaxane **220** could not be identified in the ^{1}H NMR of the product mixture. Mass spectrometry indicated that we had indeed managed to synthesise rotaxane **220**, but only in trace quantities.

Table 3.7. Trials of the CuAAC 'Click' Reaction for Rotaxane Formation[a]



Entry	Box	Time (h)	Conv. of **200** to **219** (%)[b]	Rotaxane **220** (%)[c]
1	**181**	48	100	Trace
2	-	19.5	100	-
3	**181**	1	0	-
4	-	1	45	-

[a] Reaction conditions: $CuPF_6{\cdot}(CH_3CN)_4$ (1 eq.), **181** (1 eq.), DCM, RT, 2.5 h; **200** (1 eq.), **91** (1.5 eq.), DCM, 25 °C, 0.40 M with respect to **200**. [b] Determined by ^{1}H NMR analysis of reaction mixture. [c] Determined by mass spectrometry analysis of reaction mixture.

The most likely explanation for the lack of rotaxane, that the macrocycle is not in fact bound to the metal throughout the reaction, is refuted by the result of the ligand-free control reaction (Table 3.7, entry 2). Like Leigh and co-workers,[43] we found that the ligand-free reaction reached complete conversion of acetylene **91** to non-interlocked thread **219** in only 19 hours, compared to the 48 hours required for the reactions with the bis(oxazoline) ligands. In fact, the ligand-free reaction reached 45% conversion after only 1 hour, compared to the reaction with macrocycle **167**, which saw no conversion after the same time period (Table 3.7, entries 3 and 4). The Box ligands

appear to inhibit the reaction in some fashion, possibly by preventing the lower energy, bimetallic pathway (2, Scheme 3.17, Pg. 82).

As the macrocycle is bound to the copper throughout the reaction, then the low yield of rotaxane despite complete conversion of starting materials, must be due to the thread-forming reaction taking place *outside* of the macrocycle cavity. This exocyclic process could be a result of the flexibility of macrocycle **167**, due to the length of the carbon chain which constitutes the bottom half of the macrocycle. This could conceivably fold up to one side of the bis(oxazoline) region of the macrocycle, allowing the exocyclic formation of non-interlocked thread **219** catalysed by the Box moiety of the macrocycle. As only a small amount of the macrocycles in the reaction mixture would be in the correct geometry for thread synthesis to occur *within* the macrocycle cavity, only a trace amount of rotaxane would be formed, as observed.

3.5.4. Conclusion

The CuAAC 'click' reaction was investigated as a possibility for use in the asymmetric synthesis of mechanically planar chiral rotaxanes. Bis(oxazoline) compounds were found to be suitable ligands for the reaction. Unfortunately, although macrocycle **167** was able to achieve complete conversion from staring materials to products, only trace amounts of the desired rotaxane, **220**, were synthesised. The low production of rotaxane is attributed to the flexibility of macrocycle **167**, which allows the structure to bend out of the way of the metal centre, resulting in the exocyclic formation of non-interlocked thread **219**. Redesign of the macrocycle to increase its rigidity may overcome the problem and result in a reaction which could be used in the asymmetric synthesis of planar chiral rotaxanes.

3.6. Summary and Conclusion

The Cadiot-Chodkiewicz heterocoupling reaction, the oxidative Heck reaction and the CuAAC 'click' reaction were investigated as possible reactions for the asymmetric active template synthesis of mechanically planar chiral rotaxanes. At the same time, bis(oxazoline) compounds, C_1- and C_2-symmetric, macrocyclic and non-macrocyclic, were investigated as ligands for these reactions.

In the Cadiot-Chodkiewicz heterocoupling reaction, C_2-Box ligand **179** successfully promoted the reaction to completion, producing non-symmetric thread **202** in a 74:26 ratio with homocoupled thread **203**. In contrast, non-macrocyclic C_1-Box ligand **181** and C_1-Box macrocycle **167** were found to inhibit the reaction, possibly due to a combination of steric and electronic effects.

Complete conversion from starting materials to heterocoupled thread **214** was achieved in the oxidative Heck reaction with both C_1-Box ligand **179** and C_2-Box ligand **181**. However, although the reaction with Box macrocycle **167** succeeded in producing non-symmetric thread **214**, the conversion was low (21%). Our investigations suggest that DMF competes with the Box macrocycle as a ligand for the palladium catalyst under the conditions used in the reaction.

Non-interlocked triazole thread **219** was synthesised in a 100% conversion with Box macrocycle **167**, but the desired rotaxane **220** was only formed in trace quantities. Control reactions indicate that the macrocycle is bound to the metal throughout the reaction but is unable to direct the synthesis of thread *through* the macrocycle cavity, possibly due to its flexibility.

Although macrocycle **167** proved unsuitable for the ultimate aim of synthesising planar chiral rotaxanes, the results of the model studies nevertheless provides valuable insight into the behaviour of C_1- and C_2-symmetric bis(oxazoline)s as ligands in these copper- and palladium-catalysed reactions. A more rigid macrocycle design is probably necessary for the successful synthesis of mechanically planar chiral rotaxanes *via* the asymmetric active template method. It is possible that the original macrocycle design, **138**, would have been successful in producing planar chiral rotaxanes from this method.

Chapter 4
Experimental

Chapter 4: Experimental

4.1. General Experimental Procedures

4.1.1. Solvents

Dichloromethane (DCM), acetonitrile and toluene were distilled over CaH_2 and stored over 4 Å molecular sieves. Acetone was stored over 3 Å molecular sieves. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. Anhydrous *N,N*-dimethylformamide (DMF) was used as supplied (Sureseal®). Water was distilled prior to use. All other solvents were used as supplied.

Petrol ether refers to petroleum ether bp. 40-60 °C.

4.1.2. Reagents

4,4',4''-((4-(Prop-2-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **89**,[145] 4,4',4''-((4-(3-azidopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **91**,[145]4,4',4''-((4-(5-Bromopent-4-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **106**[152] and tris(4-*tert*-butylphenyl)methanol **195**[271] were available within the group and were prepared according to literature procedures.

All other reagents used were purchased from commercial suppliers and were used without any further purification unless otherwise stated. *N*-Bromosuccinimide (NBS) was recrystallised from water. *n*-Butyl lithium was titrated with a solution (0.05 M) of 2,2,2'-trimethylpropionanilide in THF at 0 °C until the colour changed from colourless to yellow, to determine molarity. Trimethyl borate was distilled under vacuum.

18-Crown-6 refers to 1,4,7,10,13,16-hexacyclooctadecane; Grubbs 1st generation catalyst refers to bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride; Hoveyda-Grubbs' 2nd generation catalyst refers to (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium; Rochelle's salt refers to potassium sodium tartrate.

4.1.3. Reactions

Unless otherwise stated, all non-aqueous reactions were performed under a nitrogen atmosphere. All glassware was heat gun dried and cooled under vacuum before use.

4.1.4. Chromatography

Flash column chromatography, unless otherwise stated, was carried out using Silica 60A 35μm-70μm chromatography from Fisher Chemicals. Alumina flash column chromatography was carried out using activated neutral aluminium oxide Brockmann I 150 mesh from Aldrich.

Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F254 pre-coated aluminium sheets and visualized by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$, aqueous phosphomolybdic acid (PMA) or aqueous cerium ammonium molybdate (CAM) as appropriate.

4.1.5. Data Collection

Melting points were recorded on a Stuart Scientific SMP10 and are uncorrected.

Optical rotations were recorded on a Bellingham & Stanley ADP410 polarimeter. $[\alpha]_D^{temp.}$ values are reported in deg cm^2 g^{-1}, concentration (c) in g per 100 mL.

Infrared spectra were obtained on a Perkin Elmer 1600 FT IR spectrometer as potassium bromide discs; as films between sodium chloride plates; or with a Perkin Elmer Spectrum 100 FT IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution onto a diamond/ZnSe plate. Broad signals are designated as br.

^1H NMR spectra were recorded on Bruker AC 200, AV 300, DPX 400 and AV 400 spectrometers at 200, 300 and 400 MHz, respectively. Chemical shifts (δ in parts per million) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CHCl_3$, δ_H = 7.27, s; dimethyl sulfoxide, δ_H = 2.50, quin.; acetone, δ_H = 2.05, quin.). The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quarter; quin., quintet; m, multiplet. J values are given in Hertz. Assignments of numbered protons refer to the numbered structure of each compound

found in the experimental chapter. Data is reported as follows: δ (number of protons, multiplicity, *J*, assignment). In the case where mixtures of diastereisomers were inseparable, data for individual compounds is reported as far as is discernible, using ' to differentiate the diastereomers.

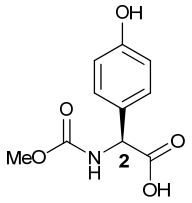
^{13}C NMR spectra were recorded on Bruker AC 200, AV 300, DPX 400 and AV 400 spectrometers at 50, 75 and 101 MHz, respectively. Chemical shifts (δ in parts per million) were referenced to residual solvent peaks ($CHCl_3$, δ_C = 77.0, t; dimethyl sulfoxide, δ_C = 39.5, septet; acetone, δ_H = 29.9, septet). Signals corresponding to C, CH, CH_2, or CH_3 groups are assigned from DEPT-135 spectroscopy. Assignments of numbered carbons refer to the numbered structure of each compound found in the experimental chapter and were determined with 2D (COSY, HMQC, NOESY) NMR spectroscopy. Data is reported as follows: δ (assignment).

Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea.

4.2. Experimental Procedures for Chapter 2

4.2.1. Procedures for the Synthesis of Amino Alcohol 142

(S)-2-(4-Hydroxyphenyl)-2-(methoxycarbonylamino)acetic acid 146[338]

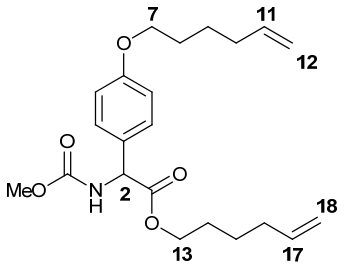


146

Methyl chloroformate (2.30 mL, 30.0 mmol) was added to a solution of 4-hydroxy-(L)-phenylglycine **147** (5.28 g, 31.6 mmol) and sodium hydrogen carbonate (8.11 g, 96.5 mmol) in 1:1 THF-H_2O (250 mL). The resulting mixture was stirred at RT for 22 h. The reaction was quenched with water (125 mL) and washed with diethyl ether. HCl (35% aq.) was added to the aqueous layer until pH 1 was reached and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was washed with toluene (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried *in vacuo* to yield the title compound **146** (6.62 g, 98%) as a white solid.

Mp 130-132 °C [lit.[338] mp 132-133 °C]; R_f 0.73 (9:1 THF-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +187.2 (*c* 0.72, MeOH) [lit.[338] $[\alpha]_D^{20}$ +197.3 (*c* 1.15, EtOH)]; ν_{max} /cm^{-1} 3381 (OH), 3204 br (OH, NH), 3033 (Ar CH), 2952 (CH), 1731 (C=O), 1655 (C=O), 1612 (Ar C=C), 1599 (Ar C=C), 1529 (NH), 1513 (Ar C=C), 1446 (Ar C=C), 1388 (OC-OH), 1360 (OH), 1269 (N-CO-O), 1219 (C-O), 1176 (Ar C-OH), 1164 (Ar CH), 1048 (N-CO-O), 909 (OC-OH), 786 (Ar CH); δ_H (200 MHz, C_2D_6SO) 7.84 (1 H, d, *J* 7.9, N*H*), 7.17 (2 H, d, *J* 8.7, Ar-*H*), 6.71 (2 H, d, *J* 8.7, Ar-*H*), 4.98 (1 H, d, *J* 7.9, *H*-2), 3.54 (3 H, s, O*CH*$_3$); δ_C (50 MHz, C_2D_6SO) 173.1 (*C*), 158.2 (*C*), 156.4 (*C*), 129.0 (*C*H), 127.2 (*C*), 113.3 (*C*H), 57.5 (*C*H), 51.6 (*C*H$_3$); Found (ESI): [M + H]$^+$ 226.0712, $C_{10}H_{12}NO_5$ requires 226.0710.

Hex-5-enyl 2-(4-(hex-5-enyloxy)phenyl)-2-(methoxycarbonylamino)acetate 149'

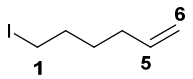


149'

6-Bromohex-1-ene **148** (7.00 mL, 52.4 mmol) was added dropwise to a stirring suspension of (*S*)-2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetic acid **146** (5.11 g, 22.7 mmol) and potassium carbonate (7.91 g, 57.2 mmol) in acetonitrile (30 mL). The resulting mixture was heated at reflux for 24 h. After cooling, the reaction was quenched with water (30 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, sat. $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 petrol ether-ethyl acetate) to yield the title compound **149'** (7.23 g, 82%) as a yellow oil.

R_f 0.32 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3429 (NH), 3059 (Ar CH), 2940 (CH), 2862 (CH), 1724 br (C=O), 1640 (C=C), 1612 (Ar C=C), 1585 (Ar C=C), 1512 (Ar C=C), 1266 (C-O-C), 1179 (C-O-C), 1057 (N-CO-O); δ_H (200 MHz, $CDCl_3$) 7.28 – 7.08 (2 H, m, Ar-*H*), 6.88 – 6.62 (2 H, m, Ar-*H*), 5.92 - 5.48 (3 H, m, *H*-11, *H*-17, N*H*), 5.20 (1 H, d, *J* 7.5, *H*-2), 5.03 - 4.77 (4 H, m, *H*-12, *H*-18), 4.04 (2 H, t, *J* 6.4, *H*-13), 3.86 (2 H, t, *J* 6.4, *H*-7), 3.58 (3 H, s, OCH_3), 2.21-1.82 (4 H, m, alkyl-*H*), 1.80-1.62 (2 H, m, alkyl-*H*), 1.60-1.37 (4 H, m, alkyl-*H*), 1.32-1.12 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 171.1 (*C*), 159.1 (*C*), 154.9 (*C*), 138.4 (*C*H), 138.1 (*C*H), 128.6 (*C*), 128.2 (*C*H), 114.7 (CH_2), 114.6 (*C*H), (plus 1 overlapping CH_2 peak), 67.6 (CH_2), 65.5 (CH_2), 57.3 (*C*H), 52.2 (CH_3), 33.3 (CH_2), 33.0 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 25.2 (CH_2), 24.7 (CH_2); Found (ESI): $[M + NH_4]^+$ 407.2543, $C_{22}H_{35}N_2O_5$ requires 407.2540.

***6-Iodohex-1-ene 150*[339]**

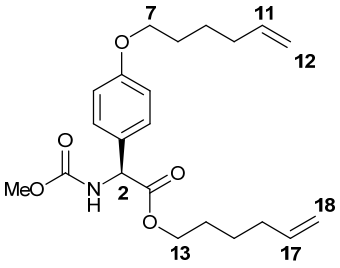


150

Sodium iodide (5.36 g, 35.8 mmol) was carefully added to a stirring solution of 6-bromohex-1-ene **148** (2.50 mL, 18.7 mmol) in acetone (100 mL) at 0 °C. The resulting mixture was heated at reflux for 23 h. After cooling, diethyl ether (100 mL) was added and the mixture was filtered. The resulting solution washed with water, 10% aq. sodium metabisulfate solution (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **150** (1.90 g, 48%) as a pale yellow liquid.

R_f 0.82 (1:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3076 (CH), 2998 (CH), 2976 (CH), 2931 (CH), 2855 (CH), 1641 (C=C), 1454 (=CH), 1428 (=CH), 1350 (=CH), 1216 (=CH), 1174 (=CH); δ_H (200 MHz, $CDCl_3$) 5.78 (1 H, ddt, *J* 17.0, 10.0, 6.2, *H*-5), 5.14 - 4.85 (2 H, m, *H*-6), 3.19 (2 H, t, *J* 7.1, *H*-1), 2.19 - 1.99 (2 H, m, alkyl-*H*), 1.94 - 1.71 (2 H, m, alkyl-*H*), 1.62 - 1.35 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 138.0 (*C*H), 114.9 (CH_2), 32.8 (CH_2), 32.5 (CH_2), 29.6 (CH_2), 6.8 (CH_2).

(S)-Hex-5-enyl 2-(4-(hex-5-enyloxy)phenyl)-2-(methoxycarbonylamino)acetate 149



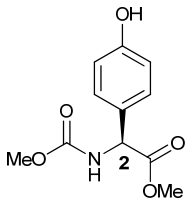
149

6-Iodohex-1-ene **150** (0.248 g, 1.18 mmol) was added dropwise to a stirring suspension of (*S*)-2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetic acid **146** (0.119 g, 0.528 mmol) and potassium carbonate (0.137 g, 0.991 mmol) in acetone (5 mL). The resulting mixture was heated at reflux for 19 h. After cooling, the reaction was quenched with water (20 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column

chromatography (4:1 petrol ether-ethyl acetate) to yield the title compound **149** (0.0095 g, 5%) as a yellow oil.

R_f 0.32 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +46.3 (*c* 0.95, $CHCl_3$); ν_{max} /cm^{-1} 3429 (NH), 3059 (Ar CH), 2940 (CH), 2862 (CH), 1724 br (C=O), 1640 (C=C), 1612 (Ar C=C), 1585 (Ar C=C), 1512 (Ar C=C), 1266 (C-O-C), 1179 (C-O-C), 1057 (N-CO-O); δ_H (200 MHz, $CDCl_3$) 7.28 – 7.08 (2 H, m, Ar-*H*), 6.88 – 6.62 (2 H, m, Ar-*H*), 5.92 - 5.48 (3 H, m, H-11, H-17, N*H*), 5.20 (1 H, d, *J* 7.5, *H*-2), 5.03 - 4.77 (4 H, m, *H*-12, *H*-18), 4.04 (2 H, t, *J* 6.4, *H*-13), 3.86 (2 H, t, *J* 6.4, *H*-7), 3.58 (3 H, s, O*CH*$_3$), 2.21-1.82 (4 H, m, alkyl-*H*), 1.80-1.62 (2 H, m, alkyl-*H*), 1.60-1.37 (4 H, m, alkyl-*H*), 1.32-1.12 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 171.1 (*C*), 159.1 (*C*), 154.9 (*C*), 138.4 (*C*H), 138.1 (*C*H), 128.6 (*C*), 128.2 (*C*H), 114.7 (*C*H_2), 114.6 (*C*H), (plus 1 overlapping *C*H_2 peak), 67.6 (*C*H_2), 65.5 (*C*H_2), 57.3 (*C*H), 52.2 (*C*H_3), 33.3 (*C*H_2), 33.0 (*C*H_2), 28.5 (*C*H_2), 27.7 (*C*H_2), 25.2 (*C*H_2), 24.7 (*C*H_2); Found (ESI): $[M + NH_4]^+$ 407.2543, $C_{22}H_{35}N_2O_5$ requires 407.2540.

(S)-Methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetate 152

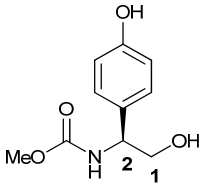


152

Thionyl chloride (24.0 mL, 329 mmol) was added dropwise to a stirring suspension of 4-hydroxy-L-phenylglycine **147** (30.8 g, 184 mmol) in methanol (560 mL). The resulting mixture was stirred at RT for 19 h. The reaction mixture was concentrated under reduced pressure and the residue washed with diethyl ether. The resulting residue was dissolved in 1:1 THF-water (500 mL) with $NaHCO_3$ (46.7 g, 556 mmol). Methyl chloroformate (16.0 mL, 207 mmol) was slowly added. The resulting mixture was stirred at 25 °C for 19 h. The reaction was quenched with water (250 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was recrystallised from ethyl acetate and petrol ether to yield the title compound **152** (41.0 g, 93%) as a white solid.

Mp 138-139 °C; R_f 0.29 (1:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{21}$ +153.5 (*c* 0.99, MeOH); ν_{max} /cm^{-1} 3371 (NH), 3279 br (OH), 3000 (CH), 2951 (CH), 2845 (CH), 1756 (C=O), 1698 (C=O),1616 (Ar C=C), 1598 (Ar C=C), 1510 (Ar C=C), 1440 (Ar C=C), 1264 (N-CO-O), 1213 (C-OH), 1171 (Ar CH), 1059 (N-CO-O), 1011 (C-OH), 780 (Ar CH); δ_H (200 MHz, C_2D_6SO) 8.00 (1 H, d, *J* 7.5, N*H*), 7.29 - 7.04 (2 H, m, Ar-*H*), 6.79 - 6.60 (2 H, m, Ar-*H*), 5.08 (1 H, d, *J* 7.5, *H*-2), 3.60 (3 H, s, OC*H*$_3$), 3.55 (3 H, s, OC*H*$_3$); δ_C (50 MHz, C_2D_6SO) 171.8 (*C*), 157.4 (*C*), 156.5 (*C*), 129.1 (*C*H), 126.4 (*C*), 115.3 (*C*H), 57.5 (*C*H), 52.1 (*C*H$_3$), 51.6 (*C*H$_3$); Found (ESI): $[M + H]^+$ 240.0869, $C_{11}H_{14}NO_5$ requires 240.0866.

(S)-Methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate 151



151

Method 1:

Borane:dimethyl sulfide complex (2.30 mL, 23.9 mmol) was added dropwise to a stirring solution of (*S*)-2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetic acid **146** (1.07 g, 4.76 mmol) in THF (50 mL) at 0 °C. The resulting mixture was stirred at RT for 22 h. The reaction was quenched with methanol (10 mL) and concentrated under reduced pressure. The resulting residue was dissolved with 9:1 chloroform-methanol (40 mL) and washed with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sat. aq. $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:1 ethyl acetate-petrol ether) to yield the title compound **151** (0.148 g, 15%) as a white solid.

Method 2:

Diisobutylaluminium hydride (98.0 mL, 98.0 mmol) was added dropwise to a stirring solution of (*S*)-methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetate **152** (5.86 g, 24.5 mmol) in THF (100 mL) at -72 °C. The resulting mixture was stirred at RT for 46 h. The reaction was then stirred at 30 °C for 72 h. The reaction was quenched with ethyl acetate (100 mL) and sat. aq. Rochelle's salt solution (100 mL) and

stirred for 23 h. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with sat. aq. Rochelle's salt solution, water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:1 ethyl acetate-petrol ether) to yield the title compound **151** (0.972 g, 19%) as a pale yellow solid.

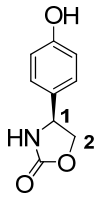
Cyclic compound (*S*)-4-(4-hydroxyphenyl)oxazolidin-2-one **153** was also formed as a side-product (1.54 g, 36%) as a pale yellow solid.

Method 3:

Lithium borohydride (2.07 g, 95.0 mmol) was added to a stirring solution of (*S*)-methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetate **152** (21.1 g, 88.0 mmol) in THF (500 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 66 h, and then heated to 40 °C for 43 h. After cooling to 0 °C, the reaction was quenched with 1.3 M aq. HCl (365 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:1 ethyl acetate-petrol ether to 9:1 ethyl acetate-petrol ether) to yield the title compound **151** (11.5 g, 62%) as a white solid. (Characterisation carried out with ethyl acetate present in sample as unable to remove residual ethyl acetate despite multiple attempts).

Mp 112-115 °C; R_f 0.20 (2:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{18}$ +70.6 (c 1.02, MeOH); ν_{max} /cm^{-1} 3339 (OH/NH), 2944 (CH), 1685 (C=O), 1600 (NH), 1534 (Ar C=C), 1517 (Ar C=C), 1452 (Ar C=C), 1360 (OH), 1218 (Ar C-O), 1173 (N-CO-O), 1058 (N-CO-O), 1013 (C-O); δ_H (300 MHz, C_2D_6SO) 7.40 (1 H, d, *J* 8.1, N*H*), 7.13 - 7.03 (2 H, m, Ar-*H*), 6.78 - 6.53 (2 H, m, Ar-*H*), 4.75 (1 H, t, *J* 5.5, O*H*), 4.46 (1 H, dt, *J* 8.1, 6.2, *H*-2), 3.50 (3 H, s, OCH_3), 3.44 (2 H, t, *J* 6.2, *H*-1); δ_C (75 MHz, C_2D_6SO) 156.8 (*C*), 156.7 (*C*), 132.1 (*C*), 128.3 (*C*H), 115.2 (*C*H), 65.3 (*C*H_2), 57.0 (*C*H), 51.6 (*C*H_3); Found (ESI): $[M + H]^+$ 212.0919, $C_{10}H_{14}NO_4$ requires 212.0917.

(S)-4-(4-Hydroxyphenyl)oxazolidin-2-one 153[340]

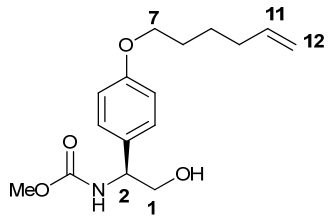


153

A solution of (*S*)-methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetate **152** (1.01 g, 4.22 mmol) in THF (10 mL) was added dropwise to a stirring suspension of Lithium aluminium hydride (0.786 g, 8.93 mmol) in THF (40 mL). The resulting mixture was stirred at RT for 18 h. The reaction was quenched with methanol (10 mL), then water (10 mL). The mixture was filtered through celite and the liquid concentrated under reduced pressure. The resulting residue was dissolved in water (50 mL) and HCl (5% aq.) added until pH 1 was reached. The mixture was extracted with ethyl acetate and chloroform. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:1 ethyl acetate-petrol ether to ethyl acetate 9:0.5:0.5 chloroform-ethyl acetate-methanol) to yield the title compound **153** (0.265 g, 35%) as a white solid.

Mp 203-205 °C [lit.[340] mp 201-204 °C]; R_f 0.32 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +48.6 (*c* 1.48, MeOH) [lit.[340] $[\alpha]_D^{20}$ +41.4 (*c* 1.7, EtOH)]; ν_{max} /cm^{-1} 3304 (NH), 3226 br (OH), 2925 (CH), 2833 (CH), 1724 (C=O), 1614 (Ar C=C), 1601 (NH), 1513 (Ar C=C), 1487 (Ar C=C), 1374 (OH), 1238 (N-CO-O), 1212 (C-O), 1029 (N-CO-O), 825 (Ar CH); δ_H (300 MHz, C_2D_6SO) 8.04 (1 H, s, N*H*), 7.19 - 7.09 (2 H, m, Ar-*H*), 6.82 - 6.72 (2 H, m, Ar-*H*), 4.81 (1 H, dd, *J* 8.6, 7.0, *H*-1a), 4.60 (1 H, dd, *J* 8.6, 8.6, *H*-2), 3.95 (1 H, dd, *J* 8.6, 7.0, *H*-1b); δ_C (75 MHz, C_2D_6SO) 158.9 (*C*), 157.2 (*C*), 131.0 (*C*), 127.4 (*C*H), 115.4 (*C*H), 71.6 (CH_2), 54.8 (*C*H); Found (ESI): $[M + H]^+$ 180.0654, $C_9H_{10}NO_3$ requires 180.0655.

(S)-Methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate 144

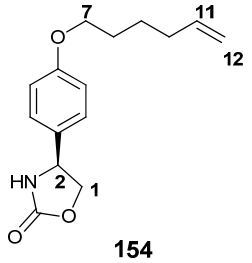


144

6-Bromohex-1-ene **148** (5.00 mL, 37.7 mmol) was added dropwise to a stirring suspension of (*S*)-methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate **151** (7.42 g, 35.1 mmol) and potassium cabonate (5.36 g, 38.8 mmol) in acetone (80 mL). The resulting mixture was heated at reflux for 43 h. After cooling, the reaction was quenched with water (80 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate-petrol ether to 9:1 ethyl acetate-petrol ether) to yield the title compound **144** (6.94 g, 68%) as a white solid.

Mp 73-74 °C; R_f 0.48 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +64.0 (*c* 1.00, $CHCl_3$); ν_{max} /cm^{-1} 3337 br (OH, NH), 2945 (CH), 2867 (CH), 1692 (C=O), 1641 (C=C), 1613 (Ar C=C), 1586 (Ar C=C), 1533 (NH), 1513 (Ar C=C), 1478 (Ar C=C), 1460 (OH), 1265 (N-CO-O), 1241 br (C-O-C), 1178 (Ar CH), 1114 (C-O-C), 1089 (C-O), 1056 (N-CO-O), 1030 (C-OH), 997 (=CH), 915 (=CH), 825 (Ar CH), 779 (OH); δ_H (200 MHz, $CDCl_3$) 7.25 - 7.16 (2 H, m, Ar-*H*), 6.96 - 6.72 (2 H, m, Ar-*H*), 5.83 (1 H, ddt, *J* 17.0, 10.4, 6.6, *H*-11), 5.37 (1 H, d, *J* 7.1, N*H*), 5.11 - 4.92 (2 H, m, *H*-12), 4.77 (1 H, dd, *J* 7.1, 5.4, *H*-2), 3.95 (2 H, t, *J* 6.2, *H*-7), 3.84 (2 H, t, *J* 5.4, *H*-1), 3.68 (3 H, s, O*C*H_3), 2.31-2.04 (3 H, m, alkyl-*H*, O*H*), 1.90 - 1.69 (2 H, m, alkyl-*H*), 1.68 - 1.46 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 158.8 (*C*), 157.1 (*C*), 138.5 (*C*H), 130.9 (C), 127.7 (*C*H), 114.8 (*C*H), (plus 1 overlapping *C*H_2 peak), 67.8 (*C*H_2), 66.6 (*C*H_2), 56.6 (*C*H), 52.4 (*C*H_3), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.3 (*C*H_2); Found (ESI): $[M + H]^+$ 294.1703, $C_{16}H_{24}NO_4$ requires 294.1700.

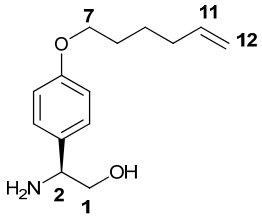
Cyclic compound (*S*)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one **154** was also formed as a side-product (2.83 g, 32%) as a white solid.



154

Mp 96-97 °C; R_f 0.68 (2:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{22}$ +28.6 (*c* 0.14, $CHCl_3$); ν_{max} /cm^{-1} 3233 (NH), 3139 (Ar CH), 2936 (CH), 2921 (CH), 1740 (C=O), 1640 (Ar C=C), 1614 (NH), 1586 (Ar C=C), 1512 (Ar C=C), 1393 (=CH), 1239 (C-O), 1061 (C-O), 1025 (N-CO-O), 925 (=CH), 828 (Ar CH); δ_H (200 MHz, $CDCl_3$) 7.33 - 7.21 (2 H, m, Ar-*H*), 6.98 - 6.85 (2 H, m, Ar-*H*), 5.84 (1 H, ddt, *J* 17.0, 10.0, 6.6, *H*-11), 5.50 (1 H, s, N*H*), 5.14 - 4.84 (3 H, m, *H*-1a, *H*-12), 4.67 (1 H, dd, *J* 8.3, 8.3, *H*-1b), 4.17 (1 H, dd, *J* 8.3, 7.1, *H*-2), 3.97 (2 H, t, *J* 6.4, *H*-7), 2.16 - 2.04 (2 H, m, alkyl-*H*), 1.90 - 1.72 (2 H, m, alkyl-*H*), 1.61 - 1.48 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 159.5 (*C*), 138.4 (*C*), 131.0 (*C*), 127.4 (*C*H), (plus 1 overlapping *C*H peak), 115.0 (*C*H), 114.8 (*C*H_2), 72.7 (*C*H_2), 67.9 (*C*H_2), 55.9 (*C*H), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.2 (*C*H_2); Found (ESI): $[M + H]^+$ 262.1441, $C_{15}H_{20}NO_3$ requires 262.1438.

(S)-2-Amino-2-(4-(hex-5-enyloxy)phenyl)ethanol 142



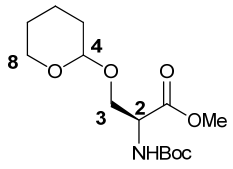
142

A suspension of (*S*)-methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate **144** (8.71 g, 29.7 mmol) and (*S*)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one **154** (2.86 g, 10.9 mmol) in a solution of potassium hydroxide (25% aq., 365 mL) was stirred at 50 °C for 27 h. After cooling, the reaction was quenched with water (365 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **142** (9.12 g, 95%) as a pale yellow solid.

Mp 72-73 °C; R_f 0.03 (20:1 DCM-methanol) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +28.3 (*c* 1.27, $CHCl_3$); ν_{max} /cm^{-1} 3500 br (OH), 3323 (NH), 3067 (Ar CH), 2936 (CH), 2865 (CH), 1713 (Ar C-H), 1642 br (C=C, NH_2), 1611 (Ar C=C), 1559 (Ar C=C), 1512 (Ar C=C), 1469 (Ar C=C), 1389 (C-N), 1245 (C-O-C), 1176 (C-N), 1155 (C-N), 1065 (Ar CH), 1028 (C-OH), 993 (=CH), 907 (=CH), 827 (Ar CH, NH_2), 809 (NH_2); δ_H (200 MHz, $CDCl_3$) 7.26 - 7.19 (2 H, m, Ar-*H*), 6.97 - 6.70 (2 H, m, Ar-*H*), 6.00 - 5.68 (1 H, m, *H*-11), 5.14 - 4.84 (2 H, m, *H*-12), 4.09 - 3.84 (3 H, m, *H*-7, *H*-2), 3.69 (1 H, dd, *J* 10.8, 4.6, *H*-1a), 3.52 (1 H, dd, *J* 10.8, 8.3, *H*-1b), 2.40 (3 H, s, NH_2, O*H*), 2.22 - 2.00 (2 H, m, alkyl-*H*), 1.91 - 1.69 (2 H, m, alkyl-*H*), 1.68 - 1.39 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 158.4 (*C*), 138.5 (*C*H), 134.4 (*C*), 127.5 (*C*H), 114.7 (*C*H), 114.5 (CH_2), 67.9 (CH_2), 67.7 (CH_2), 56.7 (*C*H), 33.4 (CH_2), 28.6 (CH_2), 25.2 (CH_2); Found (ESI): $[M + Na]^+$ 258.1467, $C_{14}H_{21}NNaO_2$ requires 258.1465.

4.2.2. Procedures for the Attempted Synthesis of Amino Alcohol 143

***Methyl (2S)-2-(tert-butoxycarbonylamino)-3-(tetrahydro-2H-pyran-2-yloxy) propanoate 158*[235]**



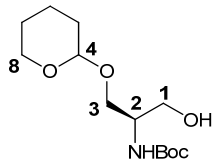
158

Dihydropyran (0.900 mL, 10.0 mmol) was added to a solution of Boc-L-serine methyl ester **159** (1.37 g, 6.27 mmol) and pyridinium *p*-toluenesulfonate (0.116 g, 0.462 mmol) in DCM (40 mL). The resulting mixture was stirred at 25 °C for 20 h. Diethyl ether (40 mL) was added and the mixture washed with brine and concentrated under reduced pressure. The resultant residue was purified by column chromatography (4:1 petrol ether-ethyl acetate) to yield the title compound **158** (1.80 g, 95%) as a white solid.

Mp 82-85 °C; R_f 0.29 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +5.4 (*c* 0.74, $CHCl_3$); ν_{max} /cm^{-1} 3322 (NH), 2945 (CH), 1732 (C=O), 1705 (N-C=O), 1524 (NH), 1249 (C-O-C), 1203 (N-CO-O), 1161 (C-O-C), 1137 (C-O-C), 1120 (CO-O-C), 1090 (C-O-C), 1057 (C-O-C), 1035 (N-CO-O), 988 (C-O-C), 811 (C-O-C); δ_H (300 MHz, $CDCl_3$) 5.55 (1 H, d, *J* 8.8, N*H*), 5.40 (1 H, d, *J* 8.6, N*H*'), 4.61 (1 H, t, *J*

3.3, *H*-4), 4.55 (1 H, t, *J* 3.9, *H*-4'), 4.52 - 4.40 (2 H, m, *H*-8a, *H*-8a'), 4.14 (1 H, dd, *J* 9.9, 3.1, *H*-3a), 3.92 (2 H, d, *J* 3.1, *H*-2, *H*-2'), 3.89 - 3.79 (1 H, m, *H*-3a'), 3.77 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3'), 3.75 - 3.65 (1 H, m, *H*-3b'), 3.62 (1 H, dd, *J* 9.9, 3.1, *H*-3b), 3.57 - 3.46 (2 H, m, *H*-8b, *H*-8b'), 1.83 - 1.44 (30 H, m, alkyl-*H*); δ_C (75 MHz, $CDCl_3$) 155.6 (*C*), (plus 1 overlapping *C* peak), 99.5 (*C*H), 98.4 (*C*H), 80.0 (*C*), (plus 1 overlapping *C* peak), 68.2 (*C*H_2), 67.4 (*C*H_2), 62.6 (*C*H_2), 61.6 (*C*H_2), 54.0 (*C*H), 53.8 (*C*H), 52.4 (*C*H_3), 52.3 (*C*H_3), 30.4 (*C*H_2), 30.1 (*C*H_2), 28.3 (*C*H_3), (plus 1 overlapping *C*H_3 peak), 25.3 (*C*H_2), 25.2 (*C*H_2), 19.4(*C*H_2), 18.9 (*C*H_2); Found (ESI): $[M + H]^+$ 304.1758, $C_{14}H_{26}NO_6$ requires 304.1755.

tert-*Butyl (2*R*)-1-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate 156*[236]



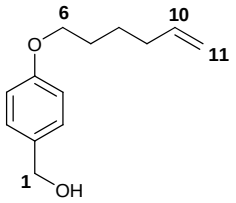
156

Diisobutylaluminium hydride (120 mL, 120 mmol) was added dropwise to a stirring solution of methyl 2-(*tert*-butoxycarbonylamino)-3-(tetrahydro-2H-pyran-2-yloxy)propanoate **158** (12.1 g, 40.0 mmol) in toluene (140 mL) at -72 °C. The resulting mixture was warmed to 0 °C and stirred for 3 h, then warmed to 25 °C for 20 h. The reaction was quenched with sat. Rochelle's salt solution (140 mL) and stirred for 3.5 h. The aqueous layer was extracted with ethyl acetate and the combined organic layers concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 petrol ether-ethyl acetate to ethyl acetate) to yield the title compound **156** (6.65g, 60%) as a yellow oil.

R_f 0.23 (1:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3474 (NH), 3348 br (OH), 2947 (CH), 1683 (C=O), 1524 (NH), 1245 (N-CO-O), 1161 (C-O-C), 1021 (C-OH), 998 (N-CO-O), 810 (C-O-C); δ_H (300 MHz, $CDCl_3$) 5.37-5.01 (2 H, m, N*H*, N*H*'), 4.66-4.40 (2 H, m, *H*-4, *H*-4'), 3.94-3.32 (14 H, m, *H*-1, *H*-1', *H*-2, *H*-2', *H*-3, *H*-3', *H*-8, *H*-8'), 1.88-1.34 (32 H, m, O*H*, O*H*', alkyl-*H*); δ_C (75 MHz, $CDCl_3$) 156.0 (*C*), (plus 1 overlapping *C* peak), 100.0 (*C*H), 99.5 (*C*H), 79.6 (*C*), (plus 1 overlapping *C*H_2 peak), 67.8 (*C*H_2), 67.5 (*C*H_2), 63.5 (*C*H_2), 63.3 (*C*H_2), 63.1 (*C*H_2), 62.8 (*C*H_2), 51.6 (*C*H), 51.5 (*C*H), 30.6 (*C*H_2), 30.5 (*C*H_2), 28.4 (*C*H_3), (plus 1

overlapping *C*H_3 peak), 25.2 (*C*H_2), (plus 1 overlapping *C*H_2 peak), 20.0 (*C*H_2), 19.7 (*C*H_2); Found (ESI): $[M + H]^+$ 276.1810, $C_{13}H_{26}NO_5$ requires 276.1805.

(4-(Hex-5-enyloxy)phenyl)methanol 161 [237]

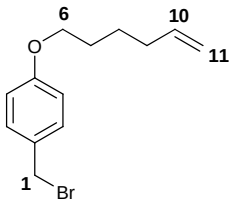


161

6-Bromo-1-hexene **148** (12.0 mL, 89.8 mmol) was added slowly to a stirring suspension of 4-hydroxybenzyl phenol **160** (10.4 g, 83.8 mmol) and potassium carbonate (22.2 g, 160 mmol) in acetone (90 mL). The resulting mixture was heated at reflux for 49 h. After cooling, the reaction was quenched with water (100 mL) and the mixture extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether-ethyl acetate to 4:1 petrol ether-ethyl acetate) to yield the title compound **161** (14.8 g, 85%) as a pale yellow oil.

R_f 0.69 (6:4 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3324 br (OH), 3076 (Ar CH, =CH), 2938 (CH), 2868 (CH), 1640 (C=C), 1612 (Ar C=C), 1584 (Ar C=C), 1511 (Ar C=C), 1472 (Ar C=C), 1438 (OH), 1245 (C-O-C), 1172 (Ar CH), 1111 (C-O-C), 1024 (C-OH), 995 (=CH), 909 (=CH), 823 (Ar CH), 731 (OH); δ_H (200 MHz, $CDCl_3$) 7.37 - 7.17 (2 H, m, Ar-*H*), 7.00 - 6.73 (2 H, m, Ar-*H*), 5.85 (1 H, ddt, *J* 16.9, 10.1, 6.6, *H*-10), 5.18 - 4.89 (2 H, m, *H*-11), 4.61 (2 H, s, *H*-1), 3.97 (2 H, t, *J* 6.4, *H*-6), 2.25 - 2.04 (2 H, m, alkyl-*H*), 1.94 - 1.41 (5 H, m, alkyl-*H*, O*H*); δ_C (50 MHz, $CDCl_3$) 158.6 (*C*), 138.5 (*C*H), 132.9 (*C*), 128.6 (*C*H), 114.7 (*C*H_2), 114.4 (*C*H), 67.7 (*C*H_2), 65.0 (*C*H_2), 33.3 (*C*H_2), 28.6 (*C*H_2), 25.2 (*C*H_2); Found (ESI): $[M + Na]^+$ 229.1199, $C_{13}H_{18}NaO_2$ requires 229.1199.

1-(Bromomethyl)-4-(hex-5-enyloxy)benzene 157

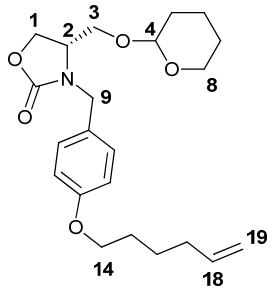


157

Phosphorous tribromide (19.5 mL, 19.5 mmol) was added dropwise to a solution of (4-(hex-5-enyloxy)phenyl)methanol **161** (3.62 g, 17.6 mmol) in DCM (70 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 h, then warmed to RT, covered in foil and stirred for 21 h. The resulting mixture was poured over ice and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **157** (3.74 g, 79%) as a yellow oil.

ν_{max} /cm^{-1} 3075 (Ar CH), 2936 (CH), 2868 (CH), 1640 (C=C), 1610 (Ar C=C), 1583 (Ar C=C), 1513 (Ar C=C), 1251 (C-O-C); δ_H (200 MHz, $CDCl_3$) 7.29 - 7.15 (2 H, m, Ar-*H*), 6.84 - 6.66 (2 H, m, Ar-*H*), 5.74 (1 H, ddt, *J* 17.1, 10.3, 6.6, *H*-10), 5.04 - 4.82 (2 H, m, *H*-11), 4.41 (2H, s, *H*-1), 3.86 (2 H, t, *J* 6.2, *H*-6), 2.15 - 1.97 (2 H, m, alkyl-*H*), 1.81 - 1.62 (2 H, m, alkyl-*H*), 1.60 - 1.37 (2 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 159.1 (*C*), 138.4 (*C*H), 130.4 (*C*H), 129.6 (*C*), 114.7 (CH_2), 114.6 (*C*H), 67.7 (CH_2), 34.1 (CH_2), 33.3 (CH_2), 28.6 (CH_2), 25.2 (CH_2); Found (GCCIP): $[M + NH_4]^+$ 286.0803, $C_{13}H_{21}{}^{79}BrNO$ requires 286.0801.

(4S)-3-(4-(Hex-5-enyloxy)benzyl)-4-((tetrahydro-2H-pyran-2-yloxy)methyl)oxazolidin-2-one 162



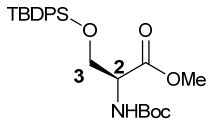
162

A solution of *tert*-butyl (2*R*)-1-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate **156** (2.62 g, 9.51 mmol) in THF (20 mL) was slowly added to a stirring

suspension of sodium hydride (0.979 g, 14.1 mmol) in THF (70 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then 1-(bromomethyl)-4-(hex-5-enyloxy)benzene **157** (3.82 g, 14 mmol) in THF (10 mL) was slowly added. The resulting mixture was warmed to RT and stirred for 20 h. The reaction was diluted with ethyl acetate (50 mL) and quenched with water (50 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2:1 petrol ether-ethyl acetate) to yield the title compound **162** (1.07 g, 29%) as a yellow oil.

R_f 0.56 (1:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +7.4 (*c* 0.54, $CHCl_3$); ν_{max} /cm^{-1} 2939 (CH), 2868 (CH), 1746 (C=O), 1640 (C=C), 1612 (Ar C=C), 1584 (Ar C=C), 1512 (Ar C=C), 1475 (Ar C=C), 1241 (N-CO-O), 1201 (Ar C-O-C), 1175 (C-O-C), 1126 (C-O-C), 1075 (C-O-C), 1034 (N-CO-O), 870 (Ar CH), 814 (C-O-C); δ_H (300 MHz, $CDCl_3$) 7.28 - 7.18 (4 H, m, Ar-*H*), 6.91 - 6.81 (4 H, m, Ar-*H*), 5.83 (2 H, ddt, *J* 17.1, 10.3, 6.6, *H*-18, *H*-18'), 5.10 - 4.92 (4 H, m, *H*-19, *H*-19'), 4.78 (1 H, d, *J* 14.9, *H*-9a), 4.71 (1 H, d, *J* 15.0, *H*-9b), 4.58 (1 H, t, *J* 3.3, *H*-4), 4.46 (1 H, t, *J* 3.3, *H*-4'), 4.33 (1 H, d, *J* 8.6, *H*-9a'), 4.28 (1 H, d, *J* 8.8, *H*-9b'), 4.21 - 4.08 (4 H, m, *H*-1, *H*-1'), 3.95 (4 H, t, *J* 6.8, *H*-14, *H*-14'), 3.86 - 3.71 (6 H, m, *H*-2, *H*-2', *H*-3a, *H*-3a', *H*-8a, *H*-8a'), 3.58 - 3.47 (2 H, m, *H*-8b, *H*-8b'), 3.46 - 3.37 (2 H, m, *H*-3b, *H*-3b'), 2.18 - 2.08 (4 H, m, alkyl-*H*), 1.90 - 1.48 (20 H, m, alkyl-*H*); δ_C (75 MHz, $CDCl_3$) 158.8 (*C*), (plus 1 overlapping *C* peak), 158.54 (*C*), 158.48 (*C*), 138.5 (*C*H), (plus 1 overlapping *C*H peak), 129.6 (*C*H), (plus 1 overlapping *C*H peak), 128.0 (*C*), 127.9 (*C*), 114.8 (CH_2), (plus 1 overlapping CH_2 peak), 114.6 (*C*H), (plus 1 overlapping *C*H peak), 99.2 (*C*H), 99.0 (*C*H), 67.8 (CH_2), (plus 1 overlapping CH_2 peak), 66.9 (CH_2), (plus 1 overlapping CH_2 peak), 66.5 (CH_2), (plus 1 overlapping CH_2 peak), 64.9 (CH_2), (plus 1 overlapping CH_2 peak), 62.4 (CH_2), 62.2 (CH_2), 54.0 (*C*H), 53.6 (*C*H), 46.1 (CH_2), 46.0 (CH_2), 33.4 (CH_2), (plus 1 overlapping CH_2 peak), 30.4 (CH_2), 30.3 (CH_2), 28.7 (CH_2), (plus 1 overlapping CH_2 peak),25.3 (CH_2), 25.2 (CH_2), 19.2 (CH_2), 19.1 (CH_2); Found (ESI): $[M + H]^+$ 464.2999, $C_{26}H_{42}NO_6$ requires 464.3007.

(S)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propanoate 163[238]

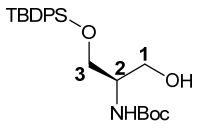


163

Imidazole (19.5 g, 325 mmol) and *tert*-butyldiphenylsilyl chloride (19.5 mL, 76.4 mmol) were added to a stirring solution of Boc-L-serine methyl ester **159** (13.9 g, 63.3 mmol) in DCM (160 mL). The resulting mixture was stirred at RT for 17h. The reaction was quenched with water (160 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (19:1 hexane-petrol ether to 4:1 hexane-ethyl acetate) to yield the title compound **163** (17.3 g, 60%) as a colourless oil.

R_f 0.30 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{21}$ +17.2 (*c* 1.16, $CHCl_3$); ν_{max} /cm^{-1} 3449 (NH), 2932 (Ar CH), 2858 (CH), 1750 (C=O), 1716 (C=O), 1590 (NH), 1496 (Ar C=C), 1473 (Ar C=C), 1249 (N-CO-O), 1163 (C-O-C), 1105 (C-O-C), 1063 (Si-O-C), 1028 (N-CO-O), 864 (Ar CH), 823 (Si-O-C); δ_H (300 MHz, $CDCl_3$) 7.66 - 7.36 (10 H, m, Ar-*H*), 5.43 (1 H, d, *J* 8.8, N*H*), 4.42 (1 H, ddd, *J* 8.8, 2.9, 2.9, *H*-2), 4.06 (1 H, dd, *J* 10.3, 2.9, *H*-3a), 3.90 (1 H, dd, *J* 10.3, 2.9, *H*-3b), 3.75 (3 H, s, OCH_3), 1.47 (9 H, s, OC(CH_3)$_3$), 1.04 (9 H, s, SiC(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 171.2 (*C*), 155.3 (*C*), 135.5 (*C*H), 132.8 (*C*), 129.8 (*C*H), 127.7 (*C*H), 79.9 (*C*), 64.6 (*C*H_2), 55.5 (*C*H), 52.3 (*C*H_3), 28.3 (*C*), 26.7 (*C*H_3), 19.3 (*C*H_3); Found (ESI): $[M + H]^+$ 458.2357, $C_{25}H_{36}NO_5Si$ requires 458.2357.

***(*R*)*-tert-*Butyl 1-(*tert*-butyldiphenylsilyloxy)-3-hydroxypropan-2-ylcarbamate 164*[238]



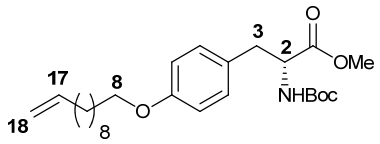
164

Lithium borohydride (0.384 g, 17.6 mmol) was added to a stirring solution of (*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propanoate **163** (16.5 g, 36.0 mmol) in THF (260 mL) at 0 °C. The resulting mixture was warmed to RT and stirred for 89 h. The reaction was cooled to 0 °C and quenched with 1.5 M aq. HCl (100 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether-ethyl acetate to 4:1 petrol ether-ethyl acetate) to yield the title compound **164** (12.8 g, 83%) as a white solid.

Mp 75-77 °C R_f 0.14 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; $[\alpha]_D^{20}$ +6.2 (*c* 0.97, $CHCl_3$); ν_{max} /cm^{-1} 3446 (OH/NH), 2956 (Ar CH), 2885 (Ar CH), 2858 (CH), 1694 (C=O), 1590 (NH), 1501 (Ar C=C), 1473 (Ar C=C), 1247 (N-CO-O), 1169 (C-O-C), 1112 (C-OH), 1055 (Si-O), 1028 (N-CO-O), 881 (Ar CH), 824 (Si-O-C); δ_H (300 MHz, $CDCl_3$) 7.71 - 7.60 (4 H, m, Ar-*H*), 7.52 - 7.35 (6 H, m, Ar-*H*), 5.09 (1 H, br. s, N*H*), 3.90 - 3.64 (5 H, m, *H*-1, *H*-2, *H*-3), 2.41 (1 H, br. s, O*H*), 1.46 (9 H, s, OC(CH_3)$_3$), 1.08 (9 H, s, SiC(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 158.8 (*C*), 135.5 (*C*H), 132.8 (*C*), 129.9 (*C*H), 127.9 (*C*H), 79.7 (*C*), 64.2 (CH_2), 63.8 (CH_2), 53.0 (*C*H), 28.4 (CH_3), 26.9 (CH_3), 19.2 (*C*); Found (ESI): $[M + H]^+$ 430.2405, $C_{24}H_{36}NO_4Si$ requires 430.2408.

4.2.3. Procedures for the Synthesis of Amino Alcohol 170

(R)-Methyl 2-(tert-butoxycarbonylamino)-3-(4-(undec-10-enyloxy)phenyl)propanoate 171

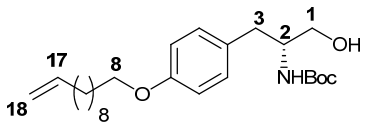


171

11-Bromoundec-1-ene **173** (2.60 mL, 11.8 mmol) was added dropwise to a stirring suspension of Boc-D-tyrosine methyl ester **172** (3.01 g, 10.2 mmol) and K_2CO_3 (2.20 g, 15.9 mmol) in acetonitrile (30 mL). The resulting mixture was heated at reflux for 23 h. After cooling, the reaction was quenched with water (30 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (19:1 petrol ether-ethyl acetate to 9:1 petrol ether-ethyl acetate) to yield the title compound **171** (3.94 g, 86%) as a white solid.

Mp 59-62 °C; R_f 0.30 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ -33.9 (*c* 1.12, $CHCl_3$); ν_{max} /cm^{-1} 3367 (NH), 2980 (Ar CH), 2920 (CH), 2851 (CH), 1737 (C=O), 1691 (C=O), 1641 (C=C), 1614 (Ar C=C), 1583 (NH), 1524 (Ar C=C), 1512 (Ar C=C), 1467 (CH), 1367 (CH), 1242 (C-O-C), 1161 (C-O-C/N-CO-O) 994 (=CH), 909 (=CH), 826 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.08 - 6.99 (2 H, m, Ar-*H*), 6.89 - 6.77 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 16.9, 10.3, 6.6, *H*-17), 5.06 - 4.90 (3 H, m, *H*-18, N*H*), 4.61 - 4.46 (1 H, m, *H*-2), 3.93 (2 H, t, *J* 6.6, *H*-8), 3.72 (3 H, s, OCH_3), 3.11 - 2.92 (2 H, m, *H*-3), 2.11 - 1.98 (2 H, m, alkyl-*H*), 1.84 - 1.68 (2 H, m, alkyl-*H*), 1.51 - 1.25 (21 H, m, alkyl-*H*, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 172.4 (*C*), 158.2 (*C*), 154.9 (*C*), 139.2 (*C*H), 130.2 (*C*H), 127.7 (*C*), 114.5 (*C*H), 114.1 (*C*H_2), 79.9 (*C*), 68.0 (*C*H_2), 54.5 (*C*H), 52.2 (*C*H_3), 37.5 (*C*H_2), 33.8 (*C*H_2), 29.5 (*C*H_2), 29.42 (*C*H_2), 29.37 (*C*H_2), 29.3 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 28.3 (*C*H_3), 26.0 (*C*H_2); Found (ESI): $[M + H]^+$ 448.3053, $C_{26}H_{42}NO_5$ requires 448.3057.

(*R*)*-tert-*Butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-ylcarbamate 174

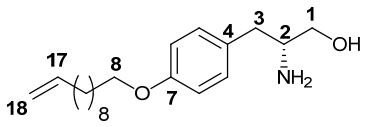


174

Lithium borohydride (0.625 g, 28.7 mmol) was added to a stirring solution of (*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(4-(undec-10-enyloxy)phenyl)propanoate **171** (16.3 g, 36.5 mmol) in THF (250 mL) at 0 °C. The resulting mixture was warmed to RT and stirred for 43 h. After cooling to 0 °C, the reaction was quenched with 1.3 M aq. HCl (142 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 petrol ether-ethyl acetate to 1:1 petrol ether-ethyl acetate) to yield the title compound **174** (13.7 g, 90%) as a white solid.

Mp 67-69 °C; R_f 0.15 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{22}$ +12.3 (*c* 2.11, $CHCl_3$); ν_{max} /cm^{-1} 3358 br (NH, OH), 2974 (Ar CH), 2920 (CH), 2852 (CH), 1689 (C=O), 1642 (Ar C=C), 1614 (Ar C=C), 1582 (NH), 1528 (Ar C=C), 1510 (Ar C=C), 1268 (N-CO-O), 1241 (C-O-C), 1171 (N-CO-O), 1061 (C-OH), 1035 (C-OH), 1004 (=CH), 906 (=CH); δ_H (300 MHz, $CDCl_3$) 7.16 - 7.08 (2 H, m, Ar-*H*), 6.89 - 6.80 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 13.2, 10.3, 6.6, *H*-17), 5.07 - 4.90 (2 H, m, *H*-18), 4.73 (1 H, d, *J* 7.7, N*H*), 3.93 (2 H, t, *J* 6.6, *H*-8), 3.88 - 3.72 (1 H, m, *H*-2), 3.72 - 3.48 (2 H, m, *H*-1), 2.78 (2 H, d, *J* 7.3, *H*-3), 2.41 (1 H, br. s, O*H*), 2.11 - 1.98 (3 H, m, alkyl-*H*), 1.85 - 1.71 (3 H, m, alkyl-*H*), 1.52 - 1.24 (19 H, m, alkyl-*H*, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 157.9 (*C*), 156.2 (*C*), 139.2 (*C*H), 130.1 (*C*H), 129.4 (*C*), 114.6 (*C*H), 114.1 (CH_2), 79.7 (*C*), 68.0 (CH_2), 64.4 (CH_2), 53.9 (*C*H), 36.2 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.42 (CH_2), 29.39 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.3 (CH_3), 26.0 (CH_2); Found (ESI): $[M + H]^+$ 420.3101, $C_{25}H_{42}NO_4$ requires 420.3108.

(R)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol 170



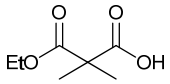
170

A solution of (*R*)-*tert*-butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-ylcarbamate **174** (13.6 g, 32.5 mmol) and *p*-toluenesulfonic acid (12.4 g, 65.1 mmol) in 1:1 DCM-THF (330 mL) was heated at reflux for 23 h. After cooling, the reaction was quenched with 1M aq. NaOH (330 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **170** (10.2 g, 98%) as a white solid.

Mp 75-78 °C; R_f 0.03 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +7.7 (*c* 1.04, $CHCl_3$); ν_{max} /cm^{-1} 3355 (NH), 3298 (NH), 3077 (Ar CH), 2923 br (OH), 2851 (CH), 1613 (Ar C=C), 1582 (Ar C=C), 1509 (Ar C=C), 1467 (Ar C=C), 1243 (C-O-C), 1059 (C-OH), 909 (=CH); δ_H (400 MHz, $CDCl_3$) 7.13 - 7.03 (2 H, m, Ar-*H*), 6.90 - 6.79 (2 H, m, Ar-*H*), 5.82 (1 H, ddt, *J* 17.0, 10.3, 6.7, *H*-17), 5.06 - 4.88 (2 H, m, *H*-18), 3.93 (2 H, t, *J* 6.5, *H*-8), 3.63 (1 H, dd, *J* 10.6, 3.2, *H*-1a), 3.37 (1 H, dd, *J* 10.6, 6.5, *H*-1b), 3.13 - 3.02 (1 H, m, *H*-2), 2.73 (1 H, dd, *J* 13.5, 5.3, *H*-3a), 2.47 (1 H, dd, *J* 13.5, 8.5, *H*-3b), 2.24 - 1.99 (5 H, m, alkyl-*H*, NH_2, O*H*), 1.85 - 1.70 (2 H, m, alkyl-*H*), 1.51 - 1.23 (12 H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 157.8 (*C*-7), 139.2 (*C*-17), 130.3 (Ar-*C*H), 130.1 (*C*-4), 114.6 (Ar-*C*H), 114.1 (*C*-18), 68.0 (*C*-8), 66.1 (*C*-1), 54.3 (*C*-2), 39.8 (alkyl-*C*H_2), 33.8 (*C*-3), 29.5 (alkyl-*C*H_2), 29.45 (alkyl-*C*H_2), 29.4 (alkyl-*C*H_2), 29.3 (alkyl-*C*H_2), 29.1 (alkyl-*C*H_2), 27.6 (alkyl-*C*H_2), 26.0 (alkyl-*C*H_2); Found (ESI): $[M + H]^+$ 320.2588, $C_{20}H_{34}NO_2$ requires 320.2584.

4.2.4. Procedures for the Synthesis of Macrocycle 167

***3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid 141*[239]**

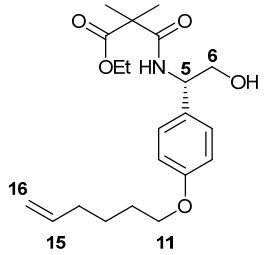


141

A solution of sodium hydroxide (2.35 g, 58.8 mmol) in water (30 mL) was added to a solution of diethyl dimethylmalonate **175** (10.2 g, 54.2 mmol) in ethanol (65 mL) at 40 °C. The resulting mixture was stirred at 40 °C for 3 h. After cooling, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in water (70 mL) and extracted with petrol ether. HCl (35% aq.) was added to the aqueous layer until pH 1 was reached then the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **141** (8.48 g, 98%) as a clear colourless liquid.

R_f 0.21 (2:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3200 br (OH), 2987 (C-H), 1705 br (C=O), 1471 (C-H), 1389 (OH), 1368 (C-OH), 1263 br (C-O), 1142 br (C-O-C), 1025 (CH), 859 (OC-OH); δ_H (400 MHz, $CDCl_3$) 4.18 (2 H, q, *J* 7.1, OCH_2CH_3), 1.42 (6 H, s, $C(CH_3)_2$), 1.25 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 178.9 (*C*), 174.1 (*C*), 61.8 (CH_2), 50.6 (*C*), 23.2 (CH_3), 14.2 (CH_3); Found (ESI): $[M + H]^+$ 161.0805, $C_7H_{13}O_4$ requires 161.0808.

(S)-Ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoate 176



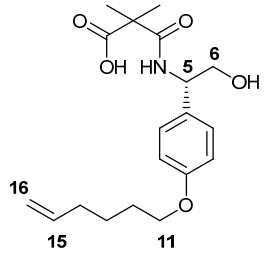
176

A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (7.26 g, 37.9 mmol) in chloroform (40 mL) was added dropwise to a solution of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **141** (6.47 g, 34.4 mmol) and 1-hydroxybenzotriazole

hydrate (5.20 g, 38.5 mmol) in chloroform (300 mL) at 0 °C. The resulting solution was stirred for 1.5 h. A solution of (*S*)-2-amino-(4-(hex-5-enyloxy)phenyl)ethanol **142** (8.90 g, 37.8 mmol) in chloroform (60 mL) was added dropwise. The resulting mixture was warmed to RT and stirred for 18 h. The reaction was quenched with 3M aq. HCl (100 mL) and the aqueous layer extracted with chloroform. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 petrol ether-ethyl acetate) to yield the title compound **176** (10.7 g, 83%) as a white solid.

Mp 73-75 °C; R_f 0.35 (1:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{19}$ +37.0 (*c* 1.08, $CHCl_3$); ν_{max} /cm^{-1} 3309 (NH), 3258 br (OH), 3074 (Ar CH), 2985 (CH), 2939 (CH), 2862 (CH), 1730 (C=O), 1644 (C=O), 1611 (Ar C=C), 1584 (Ar C=C), 1548 (NH), 1511 (Ar C=C), 1477 (Ar C=C), 1265 (C-N), 1246 (C-O-C), 1174 (C-O-C), 1151 (C-O), 1028 (C-OH), 997 (C=C), 917 (C=C), 827 (Ar CH); δ_H (200 MHz, $CDCl_3$) 7.24 - 7.09 (3 H, m, Ar-*H*, N*H*), 6.89 - 6.78 (2 H, m, Ar-*H*), 5.81 (1 H, ddt, *J* 17.0, 10.4, 6.6, *H*-15), 5.10 - 4.86 (3 H, m, *H*-5, *H*-16), 4.15 (2 H, q, *J* 7.1, O*CH*$_2$CH$_3$), 3.91 (2 H, t, *J* 6.4, *H*-11), 3.82 - 3.69 (2 H, m, *H*-6), 3.47 (1 H, s, O*H*), 2.20 - 1.96 (2 H, m, alkyl-*H*), 1.88 - 1.68 (2 H, m, alkyl-*H*), 1.64 - 1.48 (2 H, m, alkyl-*H*), 1.45 (3 H, s, C*H*$_3$), 1.42 (3 H, s, C*H*$_3$'), 1.23 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 174.6 (*C*), 172.2 (*C*), 158.4 (*C*), 138.3 (*C*H), 130.8 (*C*), 127.5 (*C*H), 114.6 (*C*H$_2$), 114.5 (*C*H), 67.5 (*C*H$_2$), 65.9 (*C*H$_2$), 61.5 (*C*H$_2$), 55.1 (*C*H), 49.7 (*C*), 33.2 (*C*H$_2$), 28.5 (*C*H$_2$), 25.1 (*C*H$_2$), 23.4 (*C*H$_3$), 13.8 (*C*H$_3$); Found (ESI): $[M + H]^+$ 378.2275, $C_{21}H_{32}NO_5$ requires 378.2275.

(S)-3-(1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoic acid 177



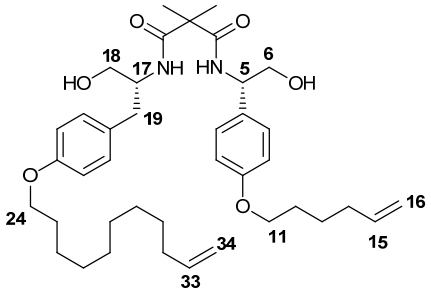
177

A solution of sodium hydroxide (2.08 g, 52.0 mmol) in 1:1 THF-water (150 mL) was added to a solution of (*S*)-ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoate **176** (6.50 g, 17.2 mmol) in 1:1 THF-water (150 mL) at

40 °C. The resulting mixture was stirred at 40 °C for 3 h. After cooling, the mixture was washed with ethyl acetate. HCl (35% aq.) was added to the aqueous layer until pH 1 was reached and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dried *in vacuo* to yield the title compound **177** (5.09 g, 86%) as a white solid.

Mp 118-121 °C; R_f 0.05 (9:1 Ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{21}$ +73.0 (*c* 1.26, $CHCl_3$); ν_{max} /cm^{-1} 3308 br (OH/NH), 2980 (Ar CH), 2935 (CH), 2865 (CH), 1715 (Ar CH), 1679 (C=O), 1655 (C=O), 1613 (Ar C=C), 1559 (NH), 1512 (Ar C=C), 1466 (Ar C=C), 1389 (C-N), 1247 (C-O-C/C-N), 1175 (C-N), 1156 (C-O), 1028 (C-OH), 992 (=CH), 900 (=CH), 827 (Ar CH), 810 (NH); δ_H (200 MHz, $CDCl_3$) 7.92 (1 H, d, *J* 5.8, N*H*), 7.20 (2 H, d, *J* 8.3, Ar-*H*), 6.82 (2 H, d, *J* 8.3, Ar-*H*), 5.83 (1 H, ddt, *J* 16.8, 10.1, 6.6, *H*-15), 5.22 - 4.92 (3 H, m, *H*-5, *H*-16), 4.04 - 3.70 (4 H, m, *H*-6, *H*-11), 2.24 - 2.04 (2 H, m, alkyl-*H*), 1.90 - 1.67 (2 H, m, alkyl-*H*), 1.65 - 1.35 (8 H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 177.2 (*C*), 173.8 (*C*), 158.6 (*C*), 138.5 (*C*H), 130.6 (*C*), 127.6 (*C*H), 114.7 (CH_2), 114.7 (*C*H), 67.7 (CH_2), 64.8 (CH_2), 55.4 (*C*H), 49.5 (*C*), 33.4 (CH_2), 28.6 (CH_2), 25.3 (CH_2), 23.5 (CH_3), 23.4 (CH_3); Found (ESI): $[M + H]^+$ 350.1965, $C_{19}H_{28}NO_5$ requires 350.1962.

***N*^{1}-((S)-1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethyl)-*N*^{3}-((R)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide 169**



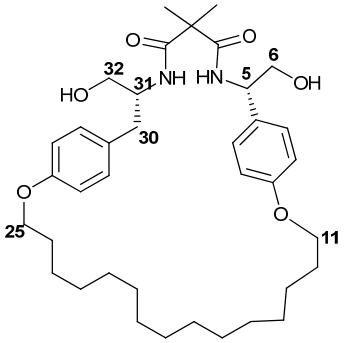
169

(*R*)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol **170** (4.31 g, 13.5 mmol) was added to a stirring solution of (*S*)-3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid **177** (4.20 g, 12.0 mmol), *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (4.30 g, 13.4 mmol) and diisopropylethylamine (2.30 mL, 13.2 mmol) in 4:1 DCM-DMF (400 mL). The

resulting mixture was stirred at RT for 93 h. The reaction was quenched with water (400 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate-petrol ether to 95:5 ethyl acetate-methanol) to yield the title compound **169** (5.70 g, 73%) as a white solid.

Mp 77-78 °C; R_f 0.47 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{20}$ +37.9 (*c* 0.95, $CHCl_3$); ν_{max} /cm^{-1} 3335 br (OH/NH), 2926 (CH), 2855 (CH), 1640 (C=O), 1613 (Ar C=C), 1583 (NH), 1510 (Ar C=C), 1471 (Ar C=C), 1243 (C-O-C), 1176 (C-O), 1034 (C-OH), 994 (=CH), 909 (=CH), 829 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.22 - 7.04 (5 H, m, Ar-H, N*H*), 6.89 - 6.78 (4 H, m, Ar-H), 6.65 (1 H, d, *J* 7.9, N*H*, N*H*'), 5.89 - 5.77 (2 H, m, *H*-15, *H*-33), 5.08 - 4.90 (5 H, m, *H*-5, *H*-16, *H*-34), 4.16 - 4.05 (1 H, m, *H*-17), 3.96 - 3.88 (4 H, m, *H*-11, *H*-24), 3.85 - 3.72 (2 H, m, *H*-6), 3.63 (1 H, dd, *J* 11.2, 3.8, *H*-18a), 3.55 (1 H, dd, *J* 11.2, 5.6, *H*-18b), 2.94 (2 H, br. s., O*H*, O*H*'), 2.82 (1 H, dd, *J* 13.8, 6.7, *H*-19a), 2.73 (1 H, dd, *J* 13.8, 7.6, *H*19b), 2.18 - 2.00 (4 H, m, alkyl-*H*), 1.84 - 1.72 (4 H, m, alkyl-*H*), 1.61 - 1.51 (2 H, m, alkyl-*H*), 1.49 - 1.28 (18 H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 158.7(Ar-*C*), 157.9 (Ar-*C*), 139.2 (*C*-15), 138.5 (*C*-33), 130.5 (Ar-*C*), 130.1 (Ar-*C*H), 129.2 (Ar-*C*), 127.6 (Ar-*C*H), 114.8 (*C*-16/*C*-34), 114.7 (Ar-*C*H), 114.6 (*C*-16/*C*-34), 114.1 (Ar-*C*H), 68.0 (*C*-11), 67.8 (*C*-24), 66.2 (*C*-6), 64.0 (*C*-18), 55.4 (*C*-5), 53.3 (*C*-17), 49.8 (*C*$(CH_3)_2$), 35.9 (*C*-19), 33.8 (alkyl-*C*H_2), 33.4 (alkyl-*C*H_2), 29.5 (alkyl-*C*H_2), 29.41 (alkyl-*C*H_2), 29.38 (alkyl-*C*H_2), 29.3 (alkyl-*C*H_2), 29.1 (alkyl-*C*H_2), 28.9 (alkyl-*C*H_2), 28.7 (alkyl-*C*H_2), 26.0 (alkyl-*C*H_2), 25.3 (alkyl-*C*H_2), 23.8 (*C*H_3), 23.6 (*C*H_3'); Found (ESI): $[M + H]^+$ 651.4362, $C_{39}H_{59}N_2O_6$ requires 651.4368.

Macrocycle 168



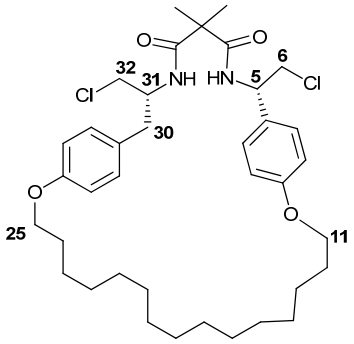
168

A solution of N^1-((*S*)-1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethyl)-N^3-((*R*)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide **169** (2.30 g, 3.53 mmol) in DCM (130 mL) was added dropwise to a stirring solution of Grubbs 1st generation catalyst (0.291 g, 0.354 mmol) in DCM (930 mL) under an argon atmosphere. The resulting mixture was heated to reflux for 7 days. The reaction was cooled to RT and concentrated under reduced pressure. The resulting residue was passed through a silica column (9:1 petrol ether-ethyl acetate to 5% methanol-ethyl acetate) to remove unreacted **169**. The resulting crude product was dissolved in THF (200 mL) and 10% w/w Pd/C (0.871 g) added. The resulting mixture was placed under a hydrogen atmosphere and stirred at RT for 6 h. The mixture was then flushed through a plug of celite with THF and the resulting solution concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate-petrol ether to 95:5 ethyl acetate-methanol) to yield the title compound **168** (1.42 g, 65%) as a white solid.

Mp 186-190 °C; R_f 0.08 (4:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or PMA dip; $[\alpha]_D^{21}$ +68.7 (*c* 0.99, $CHCl_3$); ν_{max} /cm^{-1} 3428 (NH), 3368 br. (OH), 2924 (CH), 2854 (CH), 1655 (C=O), 1633 (NH), 1611 (Ar C=C), 1582 (Ar C=C), 1530 (N-C=O), 1513 (Ar C=C), 1470 (Ar C=C), 1243 (C-N, C-O-C), 1179 (C-OH), 1073 (C-O-C), 1038 (C-O-C, C-OH), 826 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.16 - 7.07 (4 H, m, Ar-*H*), 6.94 (1 H, d, *J* 7.0, N*H*), 6.88 - 6.81 (4 H, m, Ar-*H*), 6.56 (1 H, d, *J* 7.9, N*H*'), 4.92 - 4.84 (1 H, m, *H*-5), 4.15 - 4.03 (1 H, m, *H*-31), 4.00 - 3.90 (4 H, m, *H*-11, *H*-25), 3.79 (1 H, dd, *J* 11.2, 4.4, *H*-6a), 3.74 (1 H, dd, *J* 11.2, 6.2, *H*-6b), 3.57 (1 H, dd, *J* 10.9, 3.8, *H*-32a), 3.51 (1 H, dd, *J* 10.9, 5.0, *H*-32b), 2.79 (2 H, d, *J* 7.3, *H*-30), 1.83 - 1.871 (4 H, m, alkyl-*H*), 1.60 - 1.10 (28 H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8

(*C*=O), 159.0 (Ar-*C*), 158.2 (Ar-*C*), 130.8 (Ar-*C*), 130.3 (Ar-*C*H), 129.5 (Ar-*C*), 127.7 (Ar-*C*H), 115.1 (Ar-*C*H), 115.0 (Ar-*C*H), 68.2 (*C*-11/*C*-25), 68.1 (*C*-11/*C*-25), 66.3 (*C*-6), 63.9 (*C*-32), 55.7 (*C*-5), 53.3 (*C*-31), 50.1 (*C*$(CH_3)_2$), 36.0 (*C*-30), 29.1 (alkyl-*C*H_2), 29.14 (alkyl-*C*H_2), 29.10 (alkyl-*C*H_2), 29.0 (alkyl-*C*H_2), (plus 4 overlapping *C*H_2 peaks), 28.9 (alkyl-*C*H_2), 28.8 (alkyl-*C*H_2), 28.7 (alkyl-*C*H_2), 25.9 (alkyl-*C*H_2), 25.7 (alkyl-*C*H_2), 24.2 (*C*H_3), 23.2 (*C*H_3'); Found (ESI): $[M + H]^+$ 625.4205, $C_{37}H_{57}N_2O_6$ requires 625.4211.

Macrocycle 178



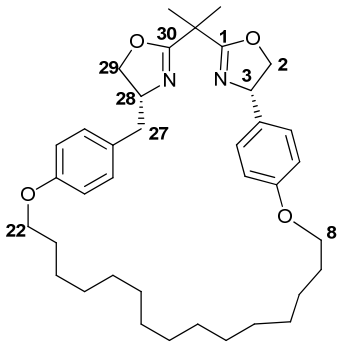
178

Thionyl chloride (2.00 mL, 27.4 mmol) was added to a stirring suspension of macrocycle **168** (1.42 g, 2.27 mmol) in DCM (50 mL). The resulting mixture was stirred at RT for 23 h. The mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM-ethyl acetate) to yield the title compound **178** (1.43 g, 94%) as a white solid.

Mp 145-148 °C; R_f 0.25 (49:1 DCM-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{21}$ +37.9 (*c* 0.58, $CHCl_3$); ν_{max} /cm^{-1} 3376 (NH), 2924 (CH), 2854 (CH), 1652 (C=O), 1612 (Ar C=C), 1584 (NH), 1510 (N-C=O), 1471 (Ar C=C), 1240 (C-O-C), 1179 (Ar CH), 1033 (C-O-C), 836 (Ar CH), 749 (C-Cl); δ_H (400 MHz, $CDCl_3$) 7.17 - 7.10 (4 H, m, Ar-*H*), 7.08 (1 H, d, *J* 7.6, N*H*), 6.94 - 6.71 (4 H, m, Ar-*H*), 6.47 (1 H, d, *J* 8.2, N*H*), 5.17 - 5.09 (1 H, m, *H*-5), 4.37 - 4.22 (1 H, m, *H*-31), 4.04 - 3.87 (4 H, m, *H*-11, *H*-25), 3.75 (2 H, d, *J* 5.6, *H*-6), 3.44 (1 H, dd, *J* 11.4, 3.5, *H*-32a), 3.38 (1 H, dd, *J* 11.4, 4.4, *H*-32b), 2.87 (1 H, dd, *J* 13.5, 5.9, *H*-30a), 2.79 (1 H, dd, *J* 13.5, 8.8, *H*-30b), 1.87 - 1.66 (4 H, m, alkyl-*H*), 1.57 - 1.25 (28 H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 173.3 (*C*=O), 172.3 (*C*=O), 158.9 (Ar-*C*), 158.2 (Ar-*C*), 130.2 (Ar-*C*), 130.1 (Ar-*C*H), 128.4 (Ar-*C*), 127.6 (Ar-*C*H), 114.9 (Ar-*C*H), 114.8 (Ar-*C*H), 67.9 (*C*-11/*C*-25), 67.8

(*C*-11/*C*-25), 53.6 (*C*-5), 51.5 (*C*-31), 49.8 (*C*(CH_3)$_2$), 47.2 (*C*-6), 45.9 (*C*-32), 36.2 (*C*-30), 29.2 (alkyl-*C*H_2), 29.11 (alkyl-*C*H_2), 29.06 (alkyl-*C*H_2), 28.9 (alkyl-*C*H_2), 28.83 (alkyl-*C*H_2), 28.79 (alkyl-*C*H_2), (plus 5 overlapping *C*H_2 peaks), 25.8 (alkyl-*C*H_2), 25.7 (alkyl-*C*H_2), 24.6 (*C*H_3), 22.3 (*C*H_3'); Found (ESI): $[M + H]^+$ 661.3533, $C_{37}H_{55}{}^{35}Cl_2N_2O_4$ requires 661.3533.

Macrocycle 167



167

Tetrabutylammonium fluoride (7.60 mL, 7.60 mmol) was added to a stirring solution of macrocycle **178** (1.25 g, 1.89 mmol) in DCM (100 mL). The resulting mixture was stirred at RT for 43 h. The mixture was concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with sat. sodium citrate (3 x 100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:1 hexane-ethyl acetate, 0.4% Et_3N) to yield the title compound **167** (0.566 g, 51%) as a white gum.

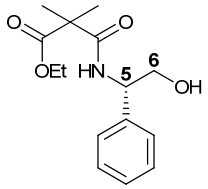
Mp 62-65 °C; R_f 0.18 (1:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or $KMnO_4$ dip; $[\alpha]_D^{21}$ -45.4 (*c* 0.44, $CHCl_3$); ν_{max} /cm^{-1} 2926 (CH), 2855 (CH), 1656 (C=N), 1612 (Ar C=C), 1583 (Ar C=C), 1512 (Ar C=C), 1472 (Ar C=C), 1247 (C-O-C), 1116 (C-O-C), 831 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.19 - 7.08 (4 H, m, Ar-*H*), 6.87 - 6.82 (4 H, m, Ar-*H*), 5.12 (1 H, dd, *J* 10.0, 6.5, *H*-3), 4.55 (1 H, dd, *J* 10.0, 8.5, *H*-2a), 4.51 - 4.43 (1 H, m, *H*-28), 4.23 (1 H, dd, *J* 9.4, 8.5, *H*-29a), 4.14 (1 H, dd, *J* 8.5, 6.5, *H*-2b), 4.04 (1 H, dd, *J* 8.5, 7.2, *H*-29b), 3.97 (4 H, t, *J* 6.5, *H*-8, *H*-22), 3.09 (1 H, dd, *J* 13.8, 5.0, *H*-27a), 2.69 (1 H, dd, *J* 13.8, 8.2, *H*-27b), 1.83 - 1.73 (4 H, m, alkyl-*H*), 1.60 (3 H, s, CH_3), 1.59 (3 H, s, CH_3'), 1.54 - 1.26 (22 H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 169.8 (*C*-1/*C*-30), 169.6 (*C*-1/*C*-30), 158.5 (Ar-*C*), 157.8 (Ar-*C*), 134.8 (Ar-*C*), 130.5 (Ar-

*C*H), 129.2 (Ar-*C*), 127.8 (Ar-*C*H), 114.8 (Ar-*C*H), 114.6 (Ar-*C*H), 75.7 (*C*-2), 71.7 (*C*-29), 68.9 (*C*-3), 68.0 (*C*-8/*C*-22), 67.8 (*C*-8/*C*-22), 67.1 (*C*-28), 40.1 (*C*-27), 38.6 ($C(CH_3)_2$), 29.31 (alkyl-CH_2), 29.28 (alkyl-CH_2), 29.2 (alkyl-CH_2), 29.14 (alkyl-CH_2), 29.09 (alkyl-CH_2), 29.05 (alkyl-CH_2), 29.00 (alkyl-CH_2), 28.96 (alkyl-CH_2), (plus 5 overlapping CH_2 peaks), 25.9 (alkyl-CH_2), 24.6 (CH_3), 23.6 (CH_3'); Found (ESI): $[M + H]^+$ 589.3987, $C_{37}H_{53}N_2O_4$ requires 589.4000.

4.3. Experimental Procedures for Chapter 3

4.3.1. Procedures for the Synthesis of Macrocycle Substitute 181

***(S)-Ethyl 3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoate 183*[245]**



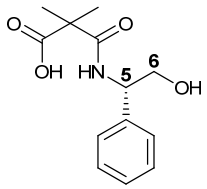
183

A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.41 g, 7.34 mmol) in chloroform (7 mL) was added dropwise to a stirring solution of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **141** (1.25 g, 6.64 mmol) and 1-hydroxybenzotriazole hydrate (0.984 g, 7.28 mmol) in chloroform (55 mL) at 0 °C. The resulting solution was stirred for 1 h. A solution of (*S*)-2-phenylglycinol **182** (1.01 g, 7.38 mmol) in chloroform (12 mL) was added dropwise. The resulting mixture was warmed to RT and stirred for 21 h. The reaction was quenched with 3 M aq. HCl (22 mL) and the aqueous layer extracted with chloroform. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 petrol ether-ethyl acetate) to yield the title compound **183** (1.31 g, 71%) as a white solid.

Mp 61-63 °C; R_f 0.32 (1:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{19}$ +66.7 (*c* 1.38, $CHCl_3$); ν_{max} /cm^{-1} 3356 (NH), 3278 br. (OH), 3064 (Ar CH), 3025 (Ar CH), 2985 (CH), 2940 (CH), 2887 (CH), 1732 (C=O), 1648 (C=O), 1586 (NH), 1544 (N-C=O), 1261 (C-O), 1147 (C-O-C), 1044 (C-OH), 906 (Ar CH), 758 (Ar CH), 698 (NH); δ_H (300 MHz, $CDCl_3$) 7.51 - 7.13 (6 H, m, Ar-H, N*H*), 5.12 - 4.99 (1 H, m, *H*-5), 4.22 (2 H, q, *J* 7.3, OCH_2CH_3), 3.97 - 3.77 (2 H, m, *H*-6), 1.52 (3 H, s,

C*H*$_3$), 1.49 (3 H, s, C*H*$_3$'), 1.28 (3 H, t, *J* 7.3, OCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 174.9 (*C*), 172.3 (*C*), 138.8 (*C*), 128.8 (*C*H), 127.8 (*C*H), 126.5 (*C*H), 66.5 (*C*H$_2$), 61.7 (*C*H$_2$), 55.8 (*C*H), 49.9 (*C*), 23.6 (*C*H$_3$), 13.9 (*C*H$_3$); Found (ESI): $[M + H]^+$ 280.1543, $C_{15}H_{22}NO_4$ requires 280.1543.

(S)-3-(2-Hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid 184[187]

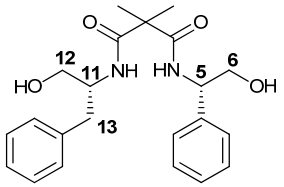


184

A solution of sodium hydroxide (0.445 g, 11.1 mmol) in water (25 mL) was added to a stirring solution of (*S*)-ethyl 3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoate **183** (0.966 g, 3.46 mmol) in THF (25 mL). The resulting mixture was heated to 40 °C for 2.5 h. The reaction was cooled to RT and HCl (35% aq.) added until pH 1 was reached. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dried *in vacuo* to yield the title compound **184** (0.775 g, 88%) as a white solid.

Mp 100-107 °C; R_f 0.01 (1:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +76.0 (*c* 1.00, $CHCl_3$); ν_{max} /cm^{-1} 3325 br. (OH), 3067 (Ar CH), 3024 (Ar CH), 2940 (CH), 2885 (CH), 2639 (CH), 1716 (C=O), 1644 (C=O), 1532 (N-C=O), 1496 (Ar C=C), 1470 (Ar C=C), 1266 (C-OH), 1157 (NH), 1030 (C-OH), 895 (C-OH), 755 (Ar CH), 698 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.65 (1 H, d, *J* 7.7, N*H*), 7.44 - 7.29 (5 H, m, Ar-*H*), 5.37 - 5.28 (1 H, m, *H*-5), 5.09 (2 H, br. s., O*H*, O*H*), 4.00 (1 H, dd, *J* 11.7, 3.7, *H*-6a), 3.85 (1 H, dd, *J* 11.7, 8.8, *H*-6b), 1.59 (3 H, s, C*H*$_3$), 1.51 (3 H, s, C*H*$_3$'); δ_C (75 MHz, $CDCl_3$) 176.8 (*C*), 174.5 (*C*), 138.6 (*C*), 128.9 (*C*H), 127.9 (*C*H), 126.4 (*C*H), 65.2 (*C*H$_2$), 56.0 (*C*H), 49.3 (*C*), 24.1 (*C*H$_3$), 23.3 (*C*H$_3$); Found (ESI): $[M + H]^+$ 252.1233, $C_{13}H_{18}NO_4$ requires 252.1230.

***N*^{1}-((S)-2-Hydroxy-1-phenylethyl)-N^{3}-((R)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide 186**

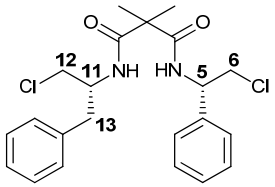


186

A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.841 g, 4.39 mmol) in chloroform (5 mL) was added dropwise to a stirring solution of (*S*)-3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid **184** (0.999 g, 3.97 mmol), 1-hydroxybenzotriazole hydrate (0.626 g, 4.63 mmol) and triethylamine (1.40 mL, 10.0 mmol) in chloroform (37 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. A solution of D-phenylalaninol **185** (0.662 g, 4.38 mmol) in chloroform (7 mL) was added dropwise. The resulting solution was warmed to RT and stirred for 41 h. The reaction was quenched with 3M aq. HCl (12 mL) and the aqueous layer extracted with chloroform. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 ethyl acetate-petrol ether) to yield the title compound **186** (1.05 g, 69%) as a pale yellow solid.

Mp 119-122 °C; R_f 0.30 (9:1 ethyl acetate-petrol ether) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{20}$ +54.9 (*c* 1.02, $CHCl_3$); ν_{max} /cm^{-1} 3315 (OH/NH), 3275 (OH/NH), 3062 (Ar CH), 2942 (CH), 1633 (C=O), 1523 (N-C=O), 1495 (Ar C=C), 1453 (Ar C=C), 1285 (C-N), 1056 (C-OH), 1032 (C-OH), 911 (Ar CH), 735 (Ar CH), 698 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.38 - 7.15 (11 H, m, Ar-*H*, N*H*), 6.67 (1 H, d, *J* 8.1, N*H*'), 5.07 - 4.93 (1 H, m, *H*-5), 4.23 - 4.06 (1 H, m, *H*-11), 3.85 (1 H, dd, *J* 11.4, 4.0, *H*-6a), 3.77 (1 H, dd, *J* 11.7, 6.6, *H*-12a), 3.63 (1 H, dd, *J* 11.7, 4.0, *H*-12b), 3.54 (1 H, dd, *J* 11.4, 5.1, *H*-6b), 2.94-2.74 (4 H, m, *H*-13, O*H*, O*H*'), 1.41 (3 H, s, CH_3), 1.35 (3 H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 174.0 (*C*), 173.8 (*C*), 138.8 (*C*), 137.5 (*C*), 129.2 (*C*H), 128.8 (*C*H), 128.5 (*C*H), 127.8 (*C*H), 126.6 (*C*H), 126.5 (*C*H), 66.0 (*C*H_2), 63.9 (*C*H_2), 55.8 (*C*H), 53.2 (*C*H), 49.8 (*C*), 36.7 (*C*H_2), 23.6 (*C*H_3), 23.5 (*C*H_3); Found (ESI): $[M + H]^+$ 385.2122, $C_{22}H_{29}N_2O_4$ requires 385.2122.

N*^{1}*-((S)-2-Chloro-1-phenylethyl)-N*^{3}*-((R)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethyl malonamide 187

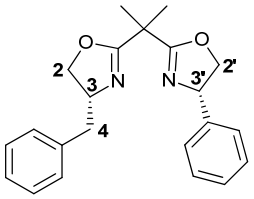


187

Thionyl chloride (1.60 mL, 21.9 mmol) was added to a stirring suspension of *N*^{1}-((*S*)-2-hydroxy-1-phenylethyl)-*N*^{3}-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **186** (0.740 g, 1.92 mmol) in DCM (40 mL). The resulting mixture was stirred at RT for 19 h. The mixture was then concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM-ethyl acetate) to yield the title compound **187** (0.681 g, 85%) as a white solid.

Mp 157-160 °C; R_f 0.64 (49:1 DCM-ethyl acetate) viewed: UV (254 nm) or CAM dip; $[\alpha]_D^{21}$ +42.3 (*c* 1.04, $CHCl_3$); ν_{max} /cm^{-1} 3310 (NH), 3063 (Ar CH), 3028 (Ar CH), 2972 (CH), 1637 (C=O), 1554 (N-C=O), 1526 (N-C=O), 1496 (Ar C=C), 1455 (Ar C=C), 699 (C-Cl); δ_H (300 MHz, $CDCl_3$) 7.43 - 7.22 (11 H, m, Ar-*H*, N*H*), 6.68 (1 H, d, *J* 8.1, N*H*'), 5.33 - 5.25 (1 H, m, *H*-5), 4.46 (1 H, tdd, *J* 7.7, 4.4, 3.7, *H*-11), 3.85 (1 H, dd, *J* 11.4, 5.1, *H*-6a), 3.78 (1 H, dd, *J* 11.4, 6.2, *H*-6b), 3.60 (1 H, dd, *J* 11.4, 4.4, *H*-12a), 3.51 (1 H, dd, *J* 11.4, 3.7, *H*-12b), 2.95 (2 H, d, *J* 7.7, *H*-13), 1.50 (3 H, s, CH_3), 1.45 (3 H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 173.3 (*C*), 172.8 (*C*), 138.3 (*C*), 136.7 (*C*), 129.2 (*C*H), 128.9 (*C*H), 128.8 (*C*H), 128.2 (*C*H), 127.0 (*C*H), 126.5 (*C*H), 54.1 (*C*H_2), 51.1 (*C*H_2), 49.5 (*C*), 47.5 (*C*H), 46.3 (*C*H), 37.4 (*C*H_2), 24.0 (*C*H_3), 23.7 (*C*H_3); Found (ESI): $[M + H]^+$ 421.1442, $C_{22}H_{27}{}^{35}Cl_2N_2O_2$ requires 421.1444.

(R)-4-Benzyl-2-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole 181



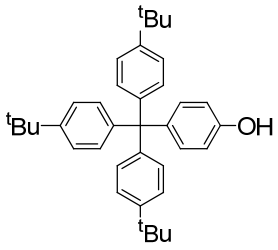
181

Tetrabutylammonium fluoride (5.50 mL, 5.50 mmol) was added to a stirring solution of N^1-((*S*)-2-chloro-1-phenylethyl)-N^3-((*R*)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **187** (0.563 g, 1.34 mmol) in THF (50 mL). The resulting mixture was stirred at RT for 18 h. The mixture was concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with sat. aq. sodium citrate (3 x 100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:3 hexane-ethyl acetate, 0.4% Et_3N) to yield the title compound **181** (0.364 g, 80%) as a colourless oil.

R_f 0.10 (3:7 hexane-ethyl acetate) viewed: UV (254 nm) or $KMnO_4$ dip; $[\alpha]_D^{20}$ -51.9 (*c* 1.31, $CHCl_3$); ν_{max} /cm^{-1} 3059 (Ar CH), 3028 (Ar CH), 2984 (CH), 2936 (CH), 2901 (CH), 1651 (N=C), 1604 (Ar C=C), 1495 (Ar C=C), 1455 (Ar C=C), 1145 (C-O), 1116 (C-O), 979 (C-N), 921 (Ar CH), 756 (Ar CH), 700 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.40 - 7.20 (10 H, m, Ar-*H*), 5.22 (1 H, dd, *J* 9.9, 7.7, *H*-3'), 4.65 (1 H, dd, *J* 10.1, 8.3, *H*-2a), 4.54 - 4.41 (1 H, m, *H*-3), 4.26 (1 H, dd, *J* 9.9, 8.8, *H*-2'a), 4.18 - 4.03 (2 H, m, *H*-2b, *H*-2'b), 3.16 (1 H, dd, *J* 13.8, 5.0, *H*-4a), 2.72 (1 H, dd, *J* 13.8, 8.6, *H*-4b), 1.63 (3 H, s, CH_3), 1.59 (3 H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 170.3 (*C*), 169.4 (*C*), 142.5 (*C*), 137.7 (*C*), 129.5 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 127.6 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 75.5 (CH_2), 72.1 (CH_2), 69.5 (*C*H), 67.1 (*C*H), 41.4 (CH_2), 38.7 (*C*), 24.4 (CH_3), (plus 1 overlapping CH_3 peak); Found (ESI): $[M + H]^+$ 349.1908, $C_{22}H_{25}N_2O_2$ requires 349.1911.

4.3.2. Procedures for the Synthesis of Stoppers

4-(Tris(4-tert-butylphenyl)methyl)phenol 196[271]

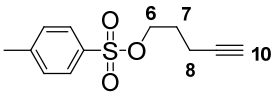


196

Tris(4-*tert*-butylphenyl)methanol **195** (11.0 g, 25.7 mmol) was added to phenol (22.6 g, 240 mmol) and the mixture heated to 50 °C. Once the phenol had melted, HCl (35% aq., 1 mL) was added and the resulting mixture heated to reflux for 19.5 h. The reaction was cooled to RT and the solid extracted with ethyl acetate and toluene. The combined organic layers were washed with 0.5 M aq. KOH (800 mL), 1M aq. HCl (100 mL) and brine. The combined aqueous layers were extracted with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was washed in refluxing hexane, cooled, filtered and washed with hexane to yield the title compound **196** (7.50 g, 62%) as a white solid.

Mp 298-300 °C [lit.[271] mp 304-306 °C]; R_f 0.51 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3485 br. (OH), 2960 (Ar CH), 1608 (Ar C=C), 1595 (Ar C=C), 1505 (Ar C=C), 1460 (Ar C=C), 1362 (C-O), 1222 (C-O), 820 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.28 - 7.22 (6 H, m, Ar-*H*), 7.15 - 7.04 (8 H, m, Ar-*H*), 6.80 - 6.65 (2 H, m, Ar-*H*), 1.33 (27 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 153.2 (*C*), 148.3 (*C*), 144.1 (*C*), 139.8 (*C*), 132.4 (*C*H), 130.7 (*C*H), 124.0 (*C*H), 113.9 (*C*H), 63.0 (*C*), 34.3 (*C*), 31.4 (*C*H$_3$); Found (ESI): $[M + NH_4]^+$ 522.3727, $C_{37}H_{48}NO$ requires 522.3730.

***Pent-4-ynyl 4-methylbenzenesulfonate 197*[341]**

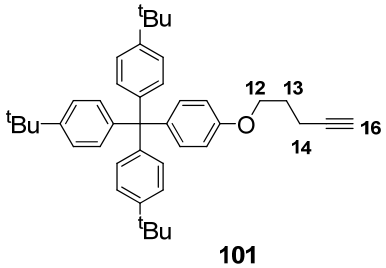


197

p-Toluenesulfonyl chloride (7.15 g, 36.8 mmol) was added to a stirring solution of pent-4-yn-1-ol **221** (3.30 mL, 34.7 mmol) and triethylamine (9.80 mL, 69.6 mmol) in DCM (100 mL) at 0 °C. The resulting mixture was stirred at RT for 21 h. The reaction was quenched with water (50 mL) and the organic layer dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 hexane-DCM to 1:1 hexane-DCM) to yield the title compound **197** (6.89 g, 83%) as a colourless oil.

R_f 0.92 (1:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or PMA dip; ν_{max} /cm^{-1} 3290 (CH), 2968 (C≡C), 1598 (Ar C=C), 1496 (Ar C=C), 1436 (Ar C=C), 1355 (S=O), 1173 (S=O), 1097 (C-O); δ_H (300 MHz, $CDCl_3$) 7.83 - 7.75 (2 H, m, Ar-*H*), 7.39 - 7.32 (2 H, m, Ar-*H*), 4.15 (2 H, t, *J* 5.9, *H*-6), 2.44 (3 H, s, CH_3), 2.25 (2 H, td, *J* 6.9, 1.7, *H*-8), 1.91 - 1.79 (3 H, m, *H*-7, *H*-10); δ_C (75 MHz, $CDCl_3$) 144.7 (*C*), 132.8 (*C*), 129.8 (*C*H), 127.8 (*C*H), 82.0 (*C*H), 69.4 (*C*), 68.7 (*C*H_2), 27.6 (*C*H_2), 21.5 (*C*H_3), 14.6 (*C*H_2); Found (ESI): $[M + NH_4]^+$ 256.1004, $C_{12}H_{18}NO_3S$ requires 256.1002.

***4,4',4''-((4-(Pent-4-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 101*[150]**



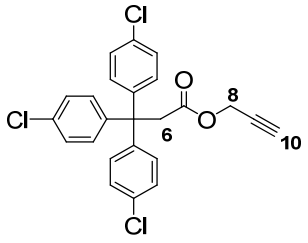
101

4-(Tris(4-*tert*-butylphenyl)methyl)phenol **196** (507 mg, 1.00 mmol), potassium carbonate (704 mg, 5.09 mmol) and 18-crown-6 (10.6 mg, 0.040 mmol) were added to a stirring solution of pent-4-ynyl 4-methylbenzenesulfonate **197** (406 mg, 1.70 mmol) in butanone (10 mL). The resulting mixture was heated at reflux for 90 h. After cooling, the reaction mixture was filtered through a sinter funnel, washing with DCM. The resulting solution was concentrated under reduced pressure and the residue was re-dissolved in DCM, washed with water, dried ($MgSO_4$) and concentrated under reduced

pressure. The resulting residue was purified by column chromatography (49:1 DCM-methanol) to yield the title compound **101** (182 mg, 32%) as a white solid.

Mp 298-300 °C [lit.[150] mp 228-230 °C]; R_f 0.88 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3485 br. (OH), 2960 (Ar CH), 1608 (Ar C=C), 1595 (Ar C=C), 1505 (Ar C=C), 1460 (Ar C=C), 1362 (C-O), 1222 (C-O), 820 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.27 - 7.21 (6 H, m, Ar-*H*), 7.14 - 7.06 (8 H, m, Ar-*H*), 6.82 - 6.75 (2 H, m, Ar-*H*), 4.06 (2 H, t, *J* 6.6, *H*-12), 2.42 (2 H, td, *J* 7.0, 2.6, *H*-14), 2.06 - 1.96 (3 H, m, *H*-13, *H*-16), 1.32 (27 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 156.7 (*C*), 148.3 (*C*), 144.1 (*C*), 139.6 (*C*), 132.2 (*C*H), 130.3 (*C*H), 124.0 (*C*H), 113.0 (*C*H), 83.6 (*C*), 68.8 (*C*H), 66.0 (*C*H$_2$), 63.1 (*C*), 34.3 (*C*), 31.4 (*C*H$_3$), 28.3 (*C*H$_2$), 15.2 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 588.4196, $C_{42}H_{54}NO$ requires 588.4200.

Prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate 200



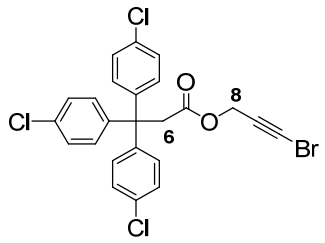
200

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.98 g, 10.3 mmol) was added to a solution of 3,3,3-tris(4-chlorophenyl)propionic acid **198** (4.03 g, 9.93 mmol) and propargyl alcohol **199** (0.600 mL, 10.3 mmol) in DCM (100 mL). 4-(Dimethylamino)pyridine (0.133 g, 1.09 mmol) was added and the resulting mixture was stirred at RT for 5 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 hexane-ethyl acetate) to yield the title compound **200** (3.67 g, 83%) as a white solid.

Mp 88-89 °C; R_f 0.55 (4: hexane-ethyl acetate) viewed: UV (254 nm); ν_{max} /cm^{-1} 3290 (≡CH), 3282 (≡CH), 3075 (Ar CH), 2948 (CH), 2129 (C≡C), 1729 (C=O), 1589 (Ar C=C), 1490 (Ar C=C), 1441 (Ar C=C), 1269 (≡CH), 1219 (Ar CH), 1137 (C-O), 1093 (Ar C-Cl), 803 (Ar CH), 688 (≡CH); δ_H (400 MHz, C_3D_6O) 7.28-7.08 (6 H, m, Ar-*H*), 7.12-6.94 (6 H, m, Ar-*H*), 4.36 (2 H, d, *J* 2.5, *H*-8), 3.61 (2 H, s, *H*-6), 2.33 (1 H, t, *J*

2.5, *H*-10); δ_C (101 MHz, C_3D_6O) 169.4 (*C*), 143.9 (*C*), 132.7 (*C*), 130.3 (*C*H), 128.3 (*C*H), 77.2 (*C*H), 74.9 (*C*), 54.6 (*C*), 52.0 (*C*H_2), 45.8 (*C*H_2); Found (ESI): $[M + Na]^+$ 465.0183, $C_{24}H_{17}{}^{35}Cl_3NaO_2$ requires 465.0186 .

3-Bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate 201

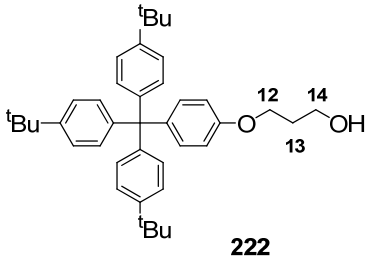


201

Silver nitrate (0.288 g, 1.69 mmol) was added to a stirring suspension of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **200** (2.00 g, 4.51 mmol) and *N*-bromosuccinimide (0.900 g, 5.06 mmol) in acetone (50 mL). The flask was protected from light and the mixture stirred at RT for 1 h. The reaction was diluted with petrol ether (50 mL) and washed with water. The aqueous layer was extracted with 1:1 petrol ether-diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **201** (2.48 g, 100%) as a white solid.

Mp 116-188 °C; R_f 0.75 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3083 (Ar CH), 2934 (CH), 2873 (CH), 2229 (C≡C), 1748 (C=O), 1591 (Ar C=C), 1490 (Ar C=C), 1326 (C-O), 1195 (Ar CH), 1183 (Ar CH), 1137 (C-O), 1092 (Ar C-Cl), 1012 (C-Br), 817 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.34 - 7.23 (6 H, m, Ar-*H*), 7.19 - 7.05 (6 H, m, Ar-*H*), 4.48 (2 H, s, *H*-8), 3.70 (2 H, s, *H*-6); δ_C (75 MHz, $CDCl_3$) 169.4 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (*C*H), 128.3 (*C*H), 73.5 (*C*), 54.6 (*C*), 52.8 (*C*H_2), 47.3 (*C*), 45.7 (*C*H_2); Found (ESI): $[M + H]^+$ 520.9479, $C_{24}H_{17}Br^{35}Cl_3O_2$ requires 520.9472.

*3-(4-(Tris(4-***tert***-butylphenyl)methyl)phenoxy)propan-1-ol 222*[342]

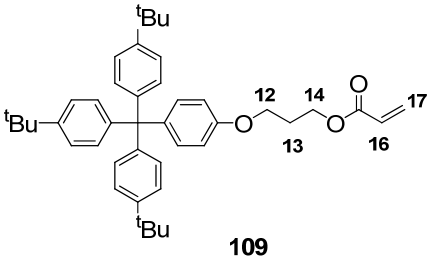


222

Potassium carbonate (2.17 g, 15.7 mmol) was added to a stirring solution of 4-(tris(4-*tert*-butylphenyl)methyl)phenol **196** (1.54 g, 3.04 mmol) and 3-bromopropan-1-ol **207** (0.410 mL, 4.53 mmol) in butanone (30 mL). The resulting mixture was heated to reflux for 40 h. After cooling, the reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (DCM) to yield the title compound **222** (1.41 g, 84%) as a white solid.

Mp 298-299 °C [lit.[342] mp > 260 °C]; R_f 0.12 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3405 br. (OH), 2959 (CH), 2901 (CH), 2867 (CH), 1578 (Ar C=C), 1505 (Ar C=C), 1471 (Ar C=C), 1248 (C-O-C), 1061 (C-O-C), 1017 (C-OH), 822 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.28 - 7.22 (6 H, m, Ar-H), 7.15 - 7.09 (8 H, m, Ar-*H*), 6.82 - 6.78 (2 H, m, Ar-*H*), 4.14 (2 H, t, *J* 5.9, *H*-12), 3.89 (2 H, dt, *J* 5.9, 5.1, *H*-14), 2.06 (2 H, quin, *J* 5.9, *H*-13), 1.80 (1 H, t, *J* 5.1, O*H*), 1.33 (27 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 139.9 (*C*), 132.3 (*C*H), 130.7 (*C*H), 124.1 (*C*H), 113.0 (*C*H), 65.8 (*C*H_2), 63.1 (*C*), 60.8 (*C*H_2), 34.3 (*C*), 32.0 (*C*H_2), 31.4 (*C*H_3); Found (ESI): $[M + NH_4]^+$ 580.4146, $C_{40}H_{54}NO_2$ requires 580.4149.

*3-(4-(Tris(4-*tert*-butylphenyl)methyl)phenoxy)propyl acrylate 109*[153]

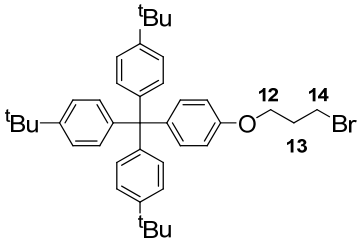


109

Triethylamine (2.50 mL, 17.9 mmol) was added to a stirring solution of 3-(4-(tris(4-*tert*-butylphenyl)methyl)phenoxy)propan-1-ol **222** (2.00 g, 3.55 mmol) in DCM (50 mL). The resulting mixture was cooled to 0 °C, then DMAP (0.0713 g, 0.584 mmol) was added, followed by acryloyl chloride **212** (0.740ml, 9.15 mmol). The resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (50 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 hexane-ethyl acetate) to yield the title compound **109** (0.850 g, 40%) as a white solid.

Mp 211-213 °C [lit.[153] mp 210-212 °C); R_f 0.88 (2:1 hexane-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 2960 (Ar CH), 2902 (CH), 2867 (CH), 1725 (C=O), 1606 (Ar C=C), 1505 (Ar C=C), 1472 (Ar C=C), 1245 (C-O-C), 1183 (C-O-C), 1061 (C-O-C), 824 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.27 - 7.20 (6 H, m, Ar-*H*), 7.13 - 7.05 (8 H, m, Ar-*H*), 6.80 - 6.74 (2 H, m, Ar-*H*), 6.41 (1 H, dd, *J* 17.2, 1.5, *H*-17a), 6.13 (1 H, dd, *J* 17.2, 10.6, *H*-16), 5.83 (1 H, dd, *J* 10.6, 1.5, *H*-17b), 4.36 (2 H, t, *J* 6.2, *H*-14), 4.05 (2 H, t, *J* 6.2, *H*-12), 2.15 (2 H, quin, *J* 6.2, *H*-13), 1.31 (27 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 166.2 (*C*), 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 139.8 (*C*), 132.3 (*C*H), 130.8 (*C*H_2), 130.7 (*C*H), 128.4 (*C*H), 124.0 (*C*H), 113.0 (*C*H), 64.1 (*C*H_2), 63.1 (*C*), 61.5 (*C*H_2), 34.3 (*C*), 31.4 (*C*H_3), 28.7 (*C*H_2); Found (ESI): $[M + NH_4]^+$ 634.4253, $C_{43}H_{56}NO_3$ requires 634.4255.

4,4',4''-((4-(3-Bromopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 119[153]

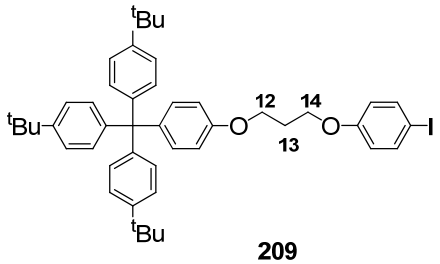


119

Diisopropyl azodicarboxylate (4.00 mL, 20.3 mmol) was added dropwise to a stirring solution of 4-(tris(4-*tert*-butylphenyl)methyl)phenol **196** (5.02 g, 9.94 mmol), triphenylphosphine (5.20 g, 19.8 mmol) and 3-bromopropan-1-ol **207** (1.80 mL, 19.9 mmol) in THF (200 mL) at 0 °C under an argon atmosphere. The resulting mixture was warmed to RT and stirred for 67 h. Triphenylphoshphine (2.72 g, 10.4 mmol) and 3-bromopropan-1-ol (0.900 mL, 9.95 mmol) were added. The resulting mixture was cooled to 0 °C and diisopropyl azodicarboxylate (2.00 mL, 10.2 mmol) was added dropwise. The reaction was heated to 25 °C for 93 h. The resulting mixture was concentrated under reduced pressure and the residue dissolved in DCM. The product was then precipitated with methanol and filtered. The resulting solid was purified by column chromatography (DCM) to yield the title compound **119** (4.46 g, 71%) as a white solid.

Mp 252-253 °C [lit.[153] mp 244-246 °C]; R_f 0.88 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 2959 (CH), 2902 (CH), 2867 (CH), 1607 (Ar C=C), 1581 (Ar C=C), 1505 (Ar C=C), 1467 (Ar C=C), 1246 (C-O-C), 824 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.32 - 7.23 (6 H, m, Ar-*H*), 7.17 - 7.08 (8 H, m, Ar-*H*), 6.85 - 6.76 (2 H, m, Ar-*H*), 4.11 (2 H, t, *J* 5.9, *H*-12), 3.64 (2 H, t, *J* 5.9, *H*-14), 2.34 (2 H, quin, *J* 5.9, *H*-13), 1.34 (27 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 156.4 (*C*), 148.3 (*C*), 144.1 (*C*), 139.8 (*C*), 132.2 (*C*H), 130.7 (*C*H), 124.0 (*C*H), 112.9 (*C*H), 65.0 (*C*), 63.0 (*C*H$_2$), 34.3 (*C*), 32.4 (*C*H$_2$), 31.4 (*C*H$_3$), 30.2 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 642.3303, $C_{40}H_{53}BrNO$ requires 642.3305.

4,4',4''-((4-(3-(4-Iodophenoxy)propoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 209[153]

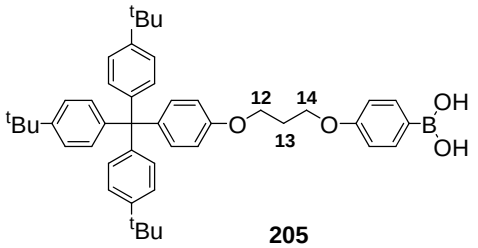


209

A suspension of 4,4',4''-((4-(3-bromopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **119** (4.41 g, 7.05 mmol), iodophenol (3.17 g, 14.4 mmol) and potassium carbonate (4.85 g, 35.1 mmol) in butanone (250 mL) was heated to 80 °C for 42 h. The reaction was cooled to RT and concentrated under reduced pressure. The resulting residue was dissolved in DCM (200 mL) and washed with 1M aq. NaOH (3 x 150 mL), water, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dissolved in DCM then precipitated with methanol. The precipitate was filtered to yield the title compound **209** (4.18 g, 78%) as a white solid.

Mp 216-219 °C [lit.[153] mp 201-203 °C]; R_f 0.14 (5:1 hexane-DCM) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3087 (Ar CH), 3031 (Ar CH), 2960 (CH), 2902 (CH), 2867 (CH), 1505 (Ar C=C), 1486 (Ar C=C), 1471 (Ar C=C), 1240 (C-O-C); δ_H (300 MHz, $CDCl_3$) 77.59 - 7.51 (2 H, m, Ar-*H*), 7.27 - 7.21 (6 H, m, Ar-*H*), 7.14 - 7.05 (8 H, m, Ar-*H*), 6.81 - 6.74 (2 H, m, Ar-*H*), 6.73 - 6.66 (2 H, m, Ar-*H*), 4.13 (4 H, t, *J* 6.2, *H*-12, *H*-14), 2.24 (2 H, quin, *J* 6.2, *H*-13), 1.31 (27 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 158.7 (*C*), 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 139.7 (*C*), 138.2 (*C*H), 132.3 (*C*H), 130.7 (*C*H), 124.0 (*C*H), 116.9 (*C*H), 112.9 (*C*H), 82.7 (*C*), 64.6 (CH_2), 64.0 (CH_2), 63.0 (*C*), 34.3 (*C*), 31.4 (CH_3), 29.2 (CH_2); Found (ESI): $[M]^+$ 782.3426, $C_{46}H_{57}INO_2$ requires 782.3428.

4-(3-(4-(Tris(4-*tert*-butylphenyl)methyl)phenoxy)propoxy)phenylboronic acid 205[153]

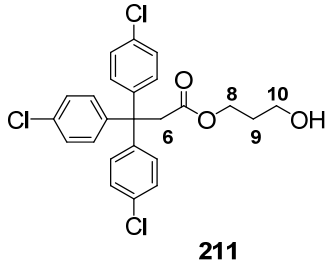


205

n-Butyl lithium (2.1 M, 0.170 mL, 0.357 mmol) was added dropwise to a stirring solution of 4,4',4''-((4-(3-(4-iodophenoxy)propoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **209** (0.133 g, 0.174 mmol) in THF (3 mL) at -78 °C. The resulting mixture was stirred for 30 min. Trimethyl borate (0.050 mL, 0.448 mmol) was added and the reaction stirred for 2 h. The reaction was stirred at RT for 39 h. The reaction was quenched with methanol (1 mL) and concentrated under reduced pressure. The resulting residue was dissolved in DCM (10 mL) and 5% aq. HCl (10 mL) added. The resulting mixture was stirred for 3.5 h. The organic layer was then washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (99:1 DCM-MeOH to 98:2 DCM-MeOH) to yield the title compound **205** (72.1 mg, 62%) as a white solid.

Mp 182-184 °C [lit.[153] mp 184-186°C]; R_f 0.43 (99:1 DCM-MeOH) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3033 (Ar CH), 2961 (CH), 2903 (CH), 2868 (CH), 1602 (Ar C=C), 1580 (Ar C=C), 1505 (Ar C=C), 1472 (Ar C=C), 1362 (CH), 1345 (B-O), 1240 (C-O-C), 1172 (B-C), 1059 (C-O-C), 822 (Ar CH); δ_H (300 MHz, $CDCl_3$) 8.25 - 8.13 (2 H, m, Ar-*H*), 7.31 - 7.24 (6 H, m, Ar-*H*), 7.19 - 7.11 (8 H, m, Ar-*H*), 7.08 - 7.03 (2 H, m, Ar-*H*), 6.87 - 6.82 (2 H, m, Ar-*H*), 5.32 (1 H, s, O*H*), 4.29 (2 H, t, *J* 5.9, *H*-12/14), 4.21 (2 H, t, *J* 5.9, *H*-12/14), 2.30 (2 H, quin, *J* 5.9, *H*-13), 1.34 (27 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 162.6 (*C*), 156.7 (*C*), (plus 1 overlapping *C* peak), 148.3 (*C*), 144.2 (*C*), 139.8 (*C*), 137.6 (*C*H), 132.3 (*C*H), 130.8 (*C*H), 124.1 (*C*H), 114.0 (*C*H), 113.0 (*C*H), 64.4 (CH_2), 64.2 (CH_2), 63.1 (*C*), 34.3 (*C*), 31.5 (CH_3), 29.4 (CH_2); Found (ESI): $[M + NH_4]^+$ 699.4576, $C_{46}H_{59}BNO_4$ requires 699.4568.

3-Hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate 211

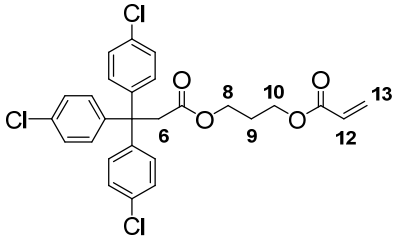


211

3,3,3-Tris(4-chlorophenyl)propanoic acid **198** (4.98 g, 12.3 mmol), 4-(dimethylamino)pyridine (0.143 g, 1.17 mmol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.35 g, 12.3 mmol) were added sequentially to a stirring solution of propane-1,3-diol (0.810 mL, 11.2 mmol) in DCM (180 mL). The resulting mixture was stirred at RT for 22 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether-ethyl acetate to 1:1 petrol ether-ethyl acetate) to yield the title compound **211** (3.48 g, 67%) as a white solid.

Mp 89-90 °C; R_f 0.05 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3401 br (OH), 3067 (Ar CH), 3032 (Ar CH), 2961 (CH), 2888 (CH), 1731 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1491 (Ar C=C), 1150 (C-O-C), 1096 (Ar C-Cl), 1053 (C-OH), 1013 (C-O-C), 811 (Ar CH), 733 (C-Cl); δ_H (300 MHz, $CDCl_3$) 7.21 - 7.15 (6 H, m, Ar-*H*), 7.12 - 7.00 (6 H, m, Ar-*H*), 3.90 (2 H, t, *J* 6.1, *H*-8), 3.56 (2 H, s, *H*-6), 3.35 (2 H, t, *J* 6.1, *H*-10), 1.54 (3 H, quin, *J* 6.1, *H*-9); δ_C (75 MHz, $CDCl_3$) 170.6 (*C*), 144.1 (*C*), 132.7 (*C*), 130.3 (*C*H), 128.3 (*C*H), 61.6 (*C*H$_2$), 59.0 (*C*H$_2$), 54.7 (*C*), 46.1 (*C*H$_2$), 31.4 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 480.0885, $C_{24}H_{25}{}^{35}Cl_3NO_3$ requires 480.0895.

3-(3,3,3-Tris(4-chlorophenyl)propanoyloxy)propyl acrylate 213



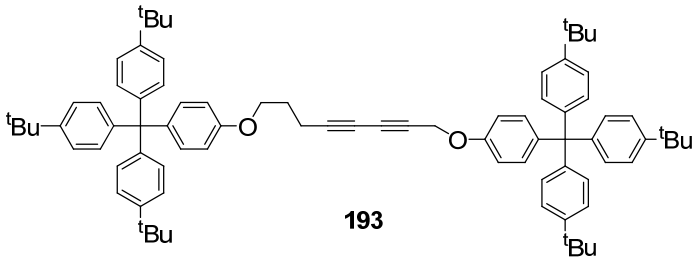
213

Triethylamine (3.80 mL, 27.3 mmol) was added to a stirring solution of 3-hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate **211** (2.73 g, 5.89 mmol) in DCM (75 mL) under an argon atmosphere. The resulting mixture was cooled to 0 °C and 4-(dimethylamino)pyridine (0.072 g, 0.590 mmol) and acrylolyl chloride **212** (1.10 mL, 13.6 mmol) were added. The resulting mixture was stirred for 2 h. The reaction was quenched with water (75 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether-ethyl acetate) to yield the title compound **213** (1.77 g, 58%) as a colourless oil.

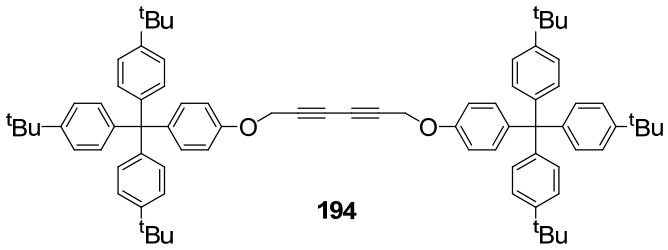
R_f 0.43 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3070 (Ar CH), 3036 (=CH), 2966 (CH), 2901 (CH), 1721 (C=O), 1636 (C=C), 1619 (Ar C=C), 1590 (Ar C=C), 1490 (Ar C=C), 1185 (C-O-C), 1147 (C-O-C), 1094 (Ar C-Cl), 985 (=CH), 907 (=CH), 811 (=CH), 730 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.23 - 7.12 (6 H, m, Ar-*H*), 7.11 - 6.98 (6 H, m, Ar-*H*), 6.31 (1 H, dd, *J* 17.6, 1.5, *H*13a), 6.01 (1 H, dd, *J* 17.6, 10.3, *H*-12), 5.74 (1 H, dd, *J* 10.3, 1.5, *H*-13b), 3.95 (2 H, t, *J* 6.3, *H*-10), 3.83 (2 H, t, *J* 6.3, *H*-8), 3.56 (2 H, s, *H*-6), 1.67 (2 H, quin, *J* 6.3, *H*-9); δ_C (75 MHz, $CDCl_3$) 170.1 (*C*), 165.9 (*C*), 144.1 (*C*), 132.6 (*C*), 130.9 (*C*H_2), 130.3 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 61.1 (*C*H_2), 60.7 (*C*H_2), 54.6 (*C*), 46.0 (*C*H_2), 27.6 (*C*H_2); Found (ESI): $[M + NH_4]^+$ 534.1002, $C_{27}H_{27}{}^{35}Cl_3NO_4$ requires 534.1000.

4.3.3. Cadiot-Chodkiewicz Reaction

Synthesis of Threads 193 and 194[152]



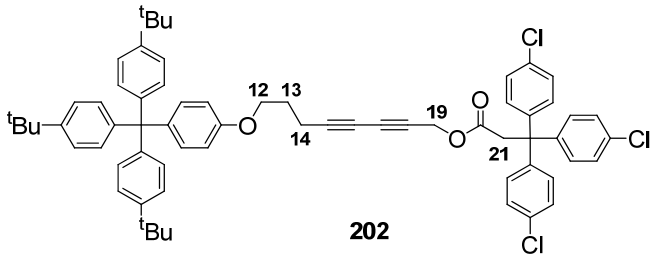
193



194

n-Butyl lithium (0.360 mL, 0.0360 mmol) was added dropwise to a stirring solution of 4,4',4''-((4-(prop-2-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **89** (0.0197 g, 0.0363 mmol) in THF (0.5 mL) at -78 °C. The resulting mixture was warmed to 0 °C and stirred for 15 min. Copper iodide (0.0087 g, 0.0457 mmol) was added and the resulting mixture warmed to RT and stirred for 15 min. The reaction mixture was cooled to -78 °C and a solution of (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) **179** (0.0136 g, 0.0407 mmol) and 4,4',4''-((4-(5-bromopent-4-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **106** (0.0251 g, 0.0386 mmol) in THF (0.9 mL) was added. The resulting mixture was stirred at RT for 20 h. The reaction was quenched with 17.5% aq. ammonia solution sat. with ethylenediaminetetraacetic acid (1 mL) and stirred under air for 50 min. The aqueous layer was extracted with DCM and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^{1}H NMR spectroscopic analysis and compared with literature values[152] to give a conversion of **89** to threads **193** and **194** of 46% and a ratio of **193**:**194** of 0.60:0.40.

General Experimental Procedure for the Synthesis of Thread 202

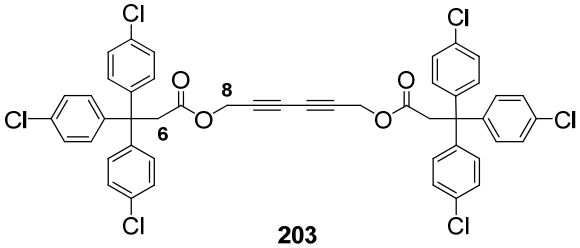


202

n-Butyl lithium (1 eq.) was added dropwise to a stirring solution of 4,4',4"-((4-(pent-4-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **101** (1 eq.) in THF (0.09 M) at -78 °C. The resulting mixture was warmed to 0 °C and stirred for 40 min. Copper iodide/chloride (1.3 eq.) was added and the resulting mixture warmed to RT and stirred for 1 h. The reaction mixture was cooled to -78 °C and a solution of Box ligand (1 eq.) and 3-bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **201** (1 eq.) in THF (0.05 M) was added. The resulting mixture was warmed to RT and stirred until reaction complete. The reaction was quenched with 17.5% aq. ammonia solution sat. with ethylenediaminetetraacetic acid and stirred under air for 40 min. The aqueous layer was extracted with DCM and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^1H NMR spectroscopic analysis (Table 3.1and Table 3.2). For characterization, a sample was purified by column chromatography (hexane to 9:1 hexane-ethyl acetate) to yield thread **202** as a white solid.

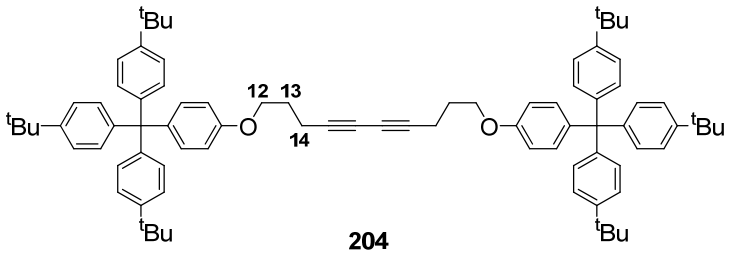
Mp 90-94 °C; R_f 0.38 (9:1 hexane-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 2962 (Ar CH), 2903 (CH), 2868 (CH), 2258 (C≡C), 1749 (C=O), 1606 (Ar C=C), 1505 (Ar C=C), 1492 (Ar C=C), 1248 (C-O-C), 1141 (C-O), 1096 (Ar C-Cl), 1054 (C-O-C), 824 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.28 - 7.23 (10 H, m, Ar-*H*), 7.17 - 7.07 (16 H, m, Ar-*H*), 6.82 - 6.75 (2 H, m, Ar-*H*), 4.51 (2 H, s, *H*-19), 4.05 (2 H, t, *J* 6.6, *H*-12), 3.68 (2 H, s, *H*-21), 2.56 (2 H, t, *J* 6.6, *H*-14), 2.04 (2 H, quin, *J* 6.6, *H*-13), 1.32 (27 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.4 (*C*), 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 143.9 (*C*), 139.8 (*C*), 132.8 (*C*), 132.3 (*C*H), 130.7 (*C*H), 130.3 (*C*H), 128.3 (*C*H), 124.0 (*C*H), 113.0 (*C*H), 81.2 (*C*), 71.7 (*C*), 68.8 (*C*), 65.8 (*C*H$_2$), 64.7 (*C*), 63.1 (*C*), 54.6 (*C*), 52.6 (*C*H$_2$), 45.8 (*C*H$_2$), 34.3 (*C*), 31.6 (*C*H$_3$), 22.7 (*C*H$_2$), 14.1 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 1028.4340, $C_{66}H_{69}{}^{35}Cl_3NO_3$ requires 1028.4338.

Threads **203** and **204**[150] were also isolated from the reaction as white solids.



203

Mp 84-88 °C; R_f 0.14 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3075 (Ar CH), 3040 (Ar CH), 2932 (CH), 2254 (C≡C), 1747 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1490 (Ar C=C), 1369 (CH), 1193 (Ar CH), 1138 (C-O), 1094 (Ar C-Cl), 808 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.34 - 7.22 (12 H, m, Ar-*H*), 7.20 - 7.09 (12 H, m, Ar-*H*), 4.54 (4 H, s, *H*-8), 3.71 (4 H, s, *H*-6); δ_C (75 MHz, $CDCl_3$) 169.3 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (*C*H), 128.4 (*C*H), 73.2 (*C*), 70.3 (*C*), 54.6 (*C*), 52.3 (*C*H$_2$), 45.7 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 900.0773, $C_{48}H_{36}{}^{35}Cl_6NO_4$ requires 900.0770.

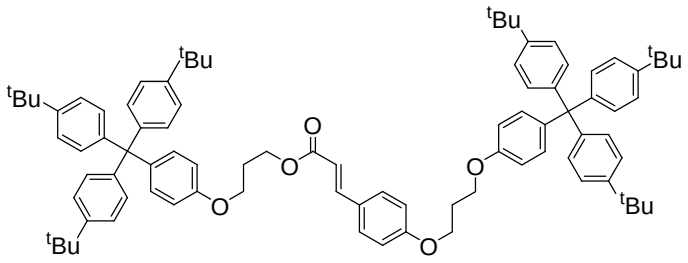


204

Mp 142-144 °C [lit.[150] mp 140 °C]; R_f 0.61 (19:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 3079 (Ar CH), 2961 (CH), 2905 (CH), 2868 (CH), 1607 (Ar C=C), 1582 (Ar C=C), 1502 (Ar C=C), 1471 (Ar C=C), 1394 (CH), 1363 (CH), 1247 (C-O-C), 1184 (CH), 1018 (C-O-C), 823 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.19 - 7.11 (12 H, m, Ar-*H*), 7.07 - 6.95 (16 H, m, Ar-*H*), 6.75 - 6.60 (4 H, m, Ar-*H*), 3.94 (4 H, t, *J* 6.2, *H*-12), 2.40 (4 H, t, *J* 6.2, *H*-14), 1.90 (4 H, quin, *J* 6.2, *H*-13), 1.22 (54 H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 156.6 (*C*), 148.3 (*C*), 144.1 (*C*), 139.4 (*C*), 132.2 (*C*H), 130.7 (*C*H), 124.1 (*C*H), 113.0 (*C*H), 65.9 (*C*), 65.7 (*C*), 63.0 (*C*), 63.0 (*C*H$_2$), 34.3 (*C*), 31.4 (*C*H$_3$), 28.2 (*C*H$_2$), 16.1 (*C*H$_2$); Found (ESI): $[M + NH_4]^+$ 1156.7901, $C_{84}H_{102}NO_2$ requires 1156.7905.

4.3.4. Oxidative Heck Reaction

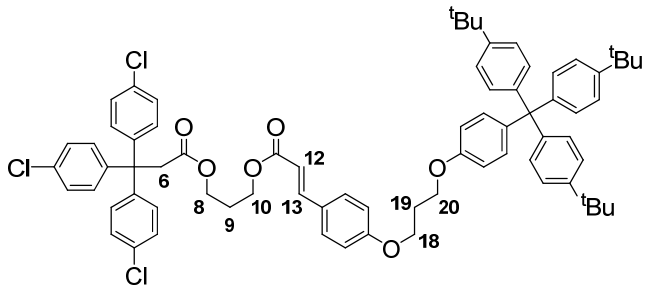
Synthesis of Thread 206[153]



206

A solution of palladium(II) acetate (0.9 mg, 0.004 mmol) and (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) **179** (7.2 mg, 0.021 mmol) in DCM (0.5 mL) was added to a stirring solution of 3-(4-(tris(4-*tert*-butylphenyl)methyl)phenoxy)propyl acrylate **109** (11.3 mg, 0.0183 mmol) and 4-(3-(4-(tris(4-*tert*-butylphenyl)methyl)phenoxy)propoxy)phenylboronic acid **205** (24.5 ,g, 0.0359 mmol) in $CHCl_3$ (0.5 mL). Benzoquinone (2.5 mg, 0.023 mmol) was added. The resulting mixture was placed under an oxygen atmosphere and stirred at RT for 92 h. The reaction was concentrated under reduced pressure. The mixture was analyzed by ^1H NMR spectroscopic analysis and compared with literature values to give a conversion of **109** to thread **206** of 35%.

General Experimental Procedure for the Synthesis of Thread 214



214

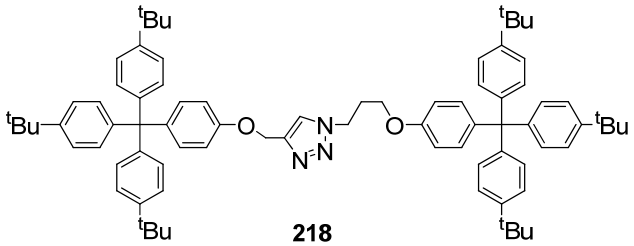
A solution of palladium(II) acetate (20 mol%) and Box ligand (1 eq.) in DMF (0.05 M) was stirred at RT for 2.5 h. A solution of 3-(3,3,3-tris(4-chlorophenyl)propanoyloxy)propyl acrylate **213** (1 eq.), 4-(3-(4-(tris(4-*tert*-butylphenyl)methyl)phenoxy)propoxy)phenylboronic acid **205** (3 eq.) and benzoquinone (1 eq.) in $CHCl_3$ (0.05 M) was added. The resulting mixture was placed under an oxygen atmosphere and heated to 25 °C for 48 h. The reaction was diluted with DCM, washed with water, dried ($MgSO_4$) and concentrated under reduced

pressure. The mixture was analyzed by ^{1}H NMR spectroscopic analysis (Table 3.3 and Table 3.4). For characterization, a sample was purified by column chromatography (19:1 petrol ether-ethyl acetate to 9:1 petrol ether-ethyl acetate) to yield thread **214** as a white solid.

Mp 164-166 °C; R_f 0.16 (9:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 2961 (Ar CH), 2905 (CH), 2868 (CH), 1738 (C=O), 1713 (C=O), 1634 (C=C), 1604 (Ar C=C), 1506 (Ar C=C), 1492 (Ar C=C), 1473 (Ar C=C), 1246 (C-O-C), 1165 (C-O), 1096 (Ar C-Cl), 1055 (C-O-C), 826 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.66 (1 H, d, *J* 15.6, *H*-13), 7.47 (2 H, s, Ar-*H*), 7.31 - 7.23 (13 H, m, Ar-*H*), 7.17 - 7.09 (13 H, m, Ar-*H*), 6.97 - 6.91 (2 H, m, Ar-*H*), 6.84 - 6.78 (2 H, m, Ar-*H*), 6.31 (1 H, d, *J* 15.6, *H*-12), 4.23 (2 H, t, *J* 6.2, *H*-20), 4.20 - 4.09 (4 H, m, *H*-8, *H*-18), 3.99 (2 H, t, *J* 6.2, *H*-10), 3.67 (2 H, s, *H*-6), 2.30 (2 H, quin, *J* 6.2, *H*-19), 1.82 (2 H, quin, *J* 6.2, *H*-9), 1.33 (27 H, s, C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 170.2 (*C*=O), 167.1 (*C*=O), 160.8 (Ar-*C*), 156.6 (Ar-*C*), 148.3 (Ar-*C*), (plus 1 overlapping *C* peak), 144.8 (Ar-*C*), 144.2 (*C*-13), 139.8 (Ar-*C*), 132.7 (Ar-*C*), 132.3 (Ar-*C*H), 130.7 (Ar-*C*H), 130.3 (Ar-*C*H), 129.8 (Ar-*C*H), 128.3 (Ar-*C*H), 127.0 (Ar-*C*), 124.1 (Ar-*C*H), 115.2 (*C*-12), 114.9 (Ar-*C*), 113.0 (Ar-*C*H), 64.7 (*C*-20), 64.0 (*C*-18), 63.1 (*C*-25), 61.4 (*C*-10), 60.7 (*C*-8), 54.6 (*C*-5), 46.1 (*C*-6), 34.3 (*C*-30), 31.4 (*C*H$_3$), 29.3 (*C*-19), 27.8 (*C*-9); Found (ESI): $[M + NH_4]^+$ 1170.4984, $C_{73}H_{79}{}^{35}Cl_3NO_6$ requires 1170.4967.

4.3.5. CuAAC Click Reaction

Synthesis of Thread 218[336]

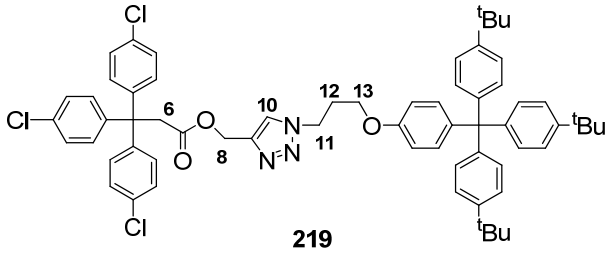


218

A solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (8.3 mg, 0.022 mmol), (*R*)-4-benzyl-2-(2-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole **181** (8.3 mg, 0.025 mmol), 4,4',4''-((4-(prop-2-ynyloxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **89** (14.2 mg, 0.0262 mmol) and 4,4',4''-((4-(3-azidopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **91** (14.8 mg,

0.0252 mmol) in DCM (2.5 mL) was placed in a sealed reaction tube. The resulting mixture was heated to 80 °C and stirred for 72 h. After cooling, the reaction was diluted with DCM (50 mL) and washed with 17.5% aq. NH_3 sat. with ethylenediaminetetraacetic acid (50 mL). The aqueous layer was extracted with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was analyzed by ^{1}H NMR spectroscopic analysis and compared with literature values to give a conversion of **89** to thread **218** of 60%.

General Experimental Procedure for the Synthesis of Thread 219



219

A solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (1 eq.) and Box ligand (1 eq.) in DCM (1 mL) was stirred for 2.5 h. A solution of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **200** (1 eq.) and 4,4',4''-((4-(3-azidopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) **91** (1 eq.) in DCM (1.5 mL) was added. The resulting mixture was concentrated under reduced pressure to the required concentration and the reaction mixture heated to 25 °C until reaction complete. The resulting mixture was diluted with DCM, washed with 17.5% aq. NH_3 sat. with ethylenediaminetetraacetic acid, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^{1}H NMR spectroscopic analysis (Table 3.5, Table 3.6 and Table 3.7). For characterization, a sample was purified by column chromatography (4:1 petrol ether-ethyl acetate to ethyl acetate) to yield thread **219** as a white solid.

Mp 129-131 °C; R_f 0.14 (4:1 petrol ether-ethyl acetate) viewed: UV (254 nm) or CAM dip; ν_{max} /cm^{-1} 2961 (Ar CH), 2903 (CH), 2868 (CH), 1739 (C=O), 1505 (Ar C=C), 1492 (Ar C=C), 1401 (N=N), 1363 (N=N), 1245 (C-O-C), 1185 (C-O-C), 1146 (C-O-C), 1110 (C-N), 1096 (Ar C-Cl), 1055 (C-O-C), 822 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.28 - 7.19 (13 H, m, Ar-*H*), 7.15 - 7.06 (14 H, m, *H*-10, Ar-*H*), 6.81 - 6.72 (2 H, m, Ar-*H*), 5.00 (2 H, s, *H*-8), 4.58 (2 H, t, *J* 6.3, *H*-11), 3.96 (2 H, t, *J* 6.3, *H*-13), 3.68 (2 H, s, *H*-6), 2.38 (2 H, quin, *J* 6.3, *H*-12), 1.33 (27 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 170.2 (C),

156.2 (C), 148.4 (C), 144.1 (C), 144.0 (C), 142.1 (C), 140.2 (C), 132.6 (CH), 132.4 (C), 130.7 (CH), 130.3 (CH), 128.2 (CH), 124.1 (CH), (plus 1 overlapping *C*H peak), 112.9 (CH), 63.8 (C), 63.1 (CH_2), 57.8 (CH_2), 54.5 (C), 47.3 (CH_2), 46.0 (CH_2), 34.3 (C), 31.4 (CH_3), 30.0 (CH_2); Found (ESI): $[M + H]^+$ 1030.4244, $C_{64}H_{67}{}^{35}Cl_3N_3O_3$ requires 1030.4243.

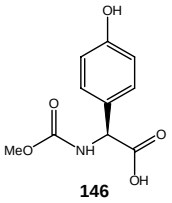
Appendix A

^{1}H and ^{13}C NMR Spectra of Prepared Compounds

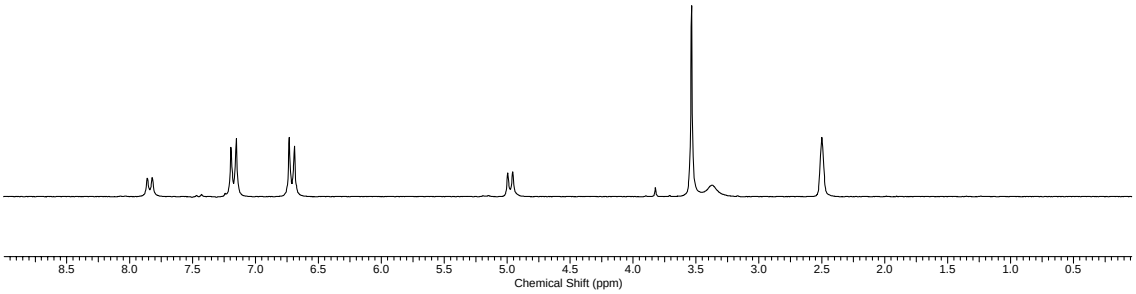
(S)-2-(4-Hydroxyphenyl)-2-(methoxycarbonylamino)acetic acid 146

PEG-1-008-H.esp

^{1}H NMR (200 MHz, C_2D_6SO)

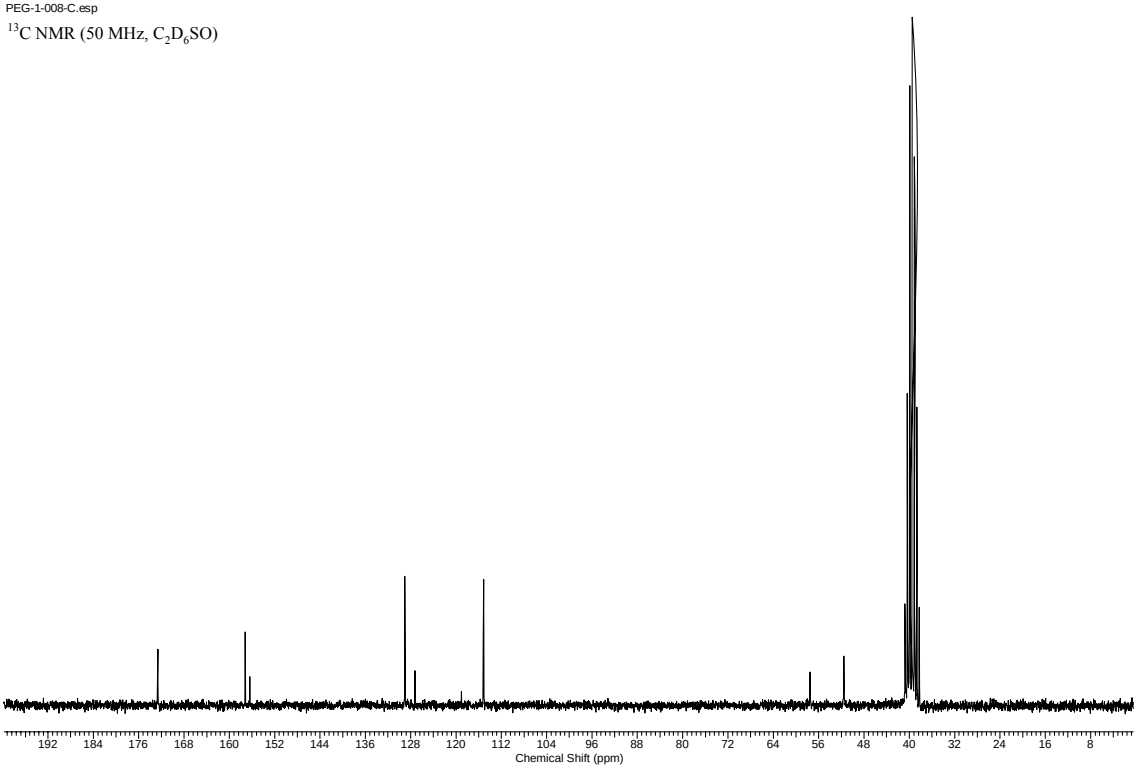


146



PEG-1-008-C.esp

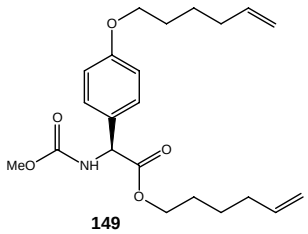
^{13}C NMR (50 MHz, C_2D_6SO)



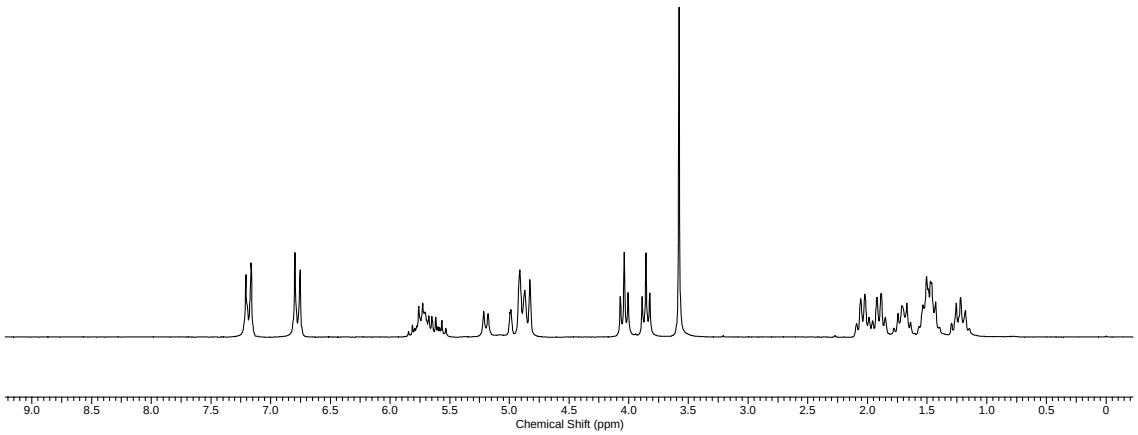
(S)-Hex-5-enyl 2-(4-(hex-5-enyloxy)phenyl)-2-(methoxycarbonylamino)acetate 149

PEG-1-013-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

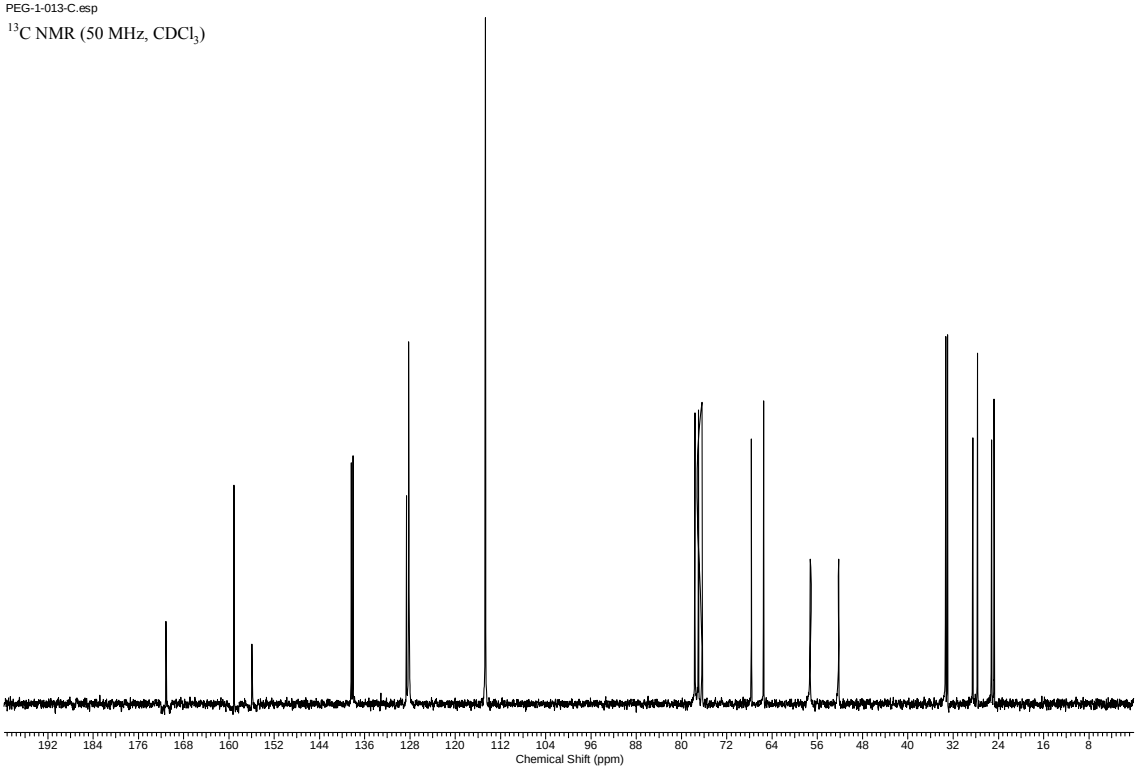


149



PEG-1-013-C.esp

^{13}C NMR (50 MHz, $CDCl_3$)

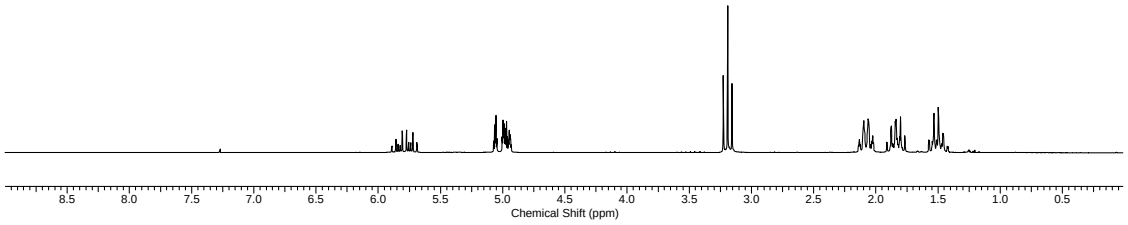


6-Iodohex-1-ene 150

PEG-1-050-H.esp

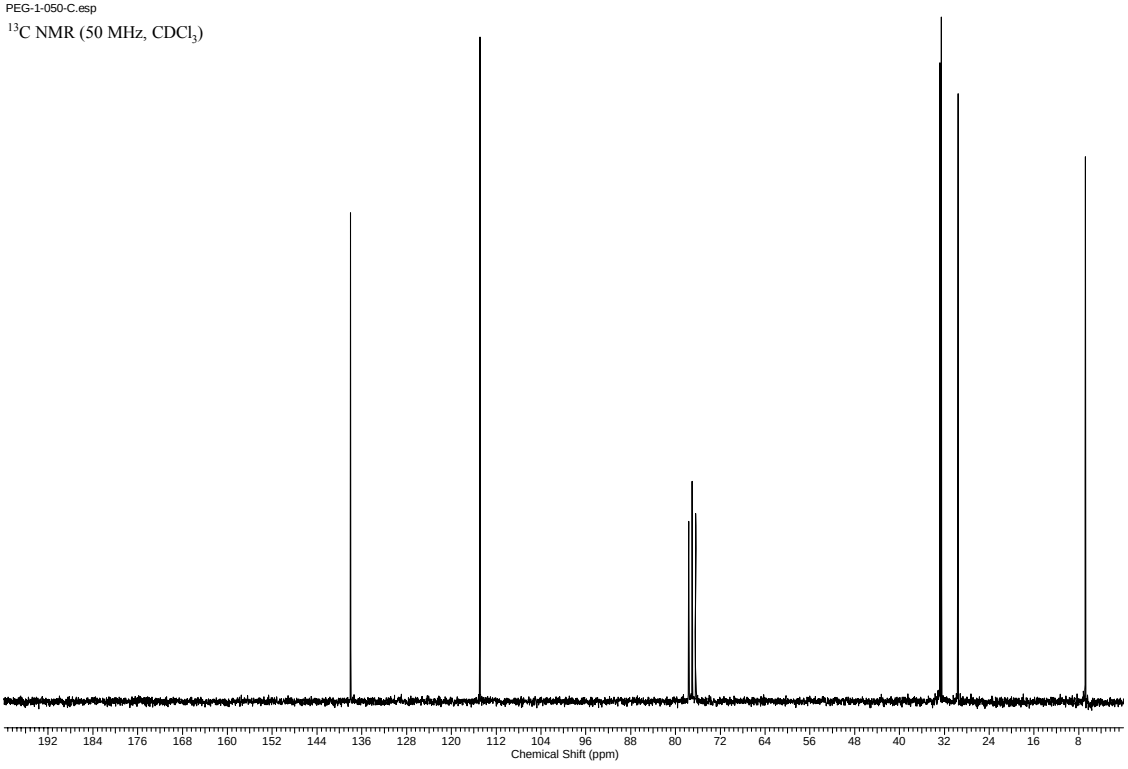
^{1}H NMR (200 MHz, $CDCl_3$)

150



PEG-1-050-C.esp

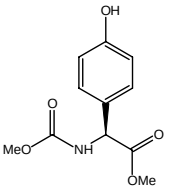
^{13}C NMR (50 MHz, $CDCl_3$)



(S)-Methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino)acetate 152

PEG-1-070-H.esp

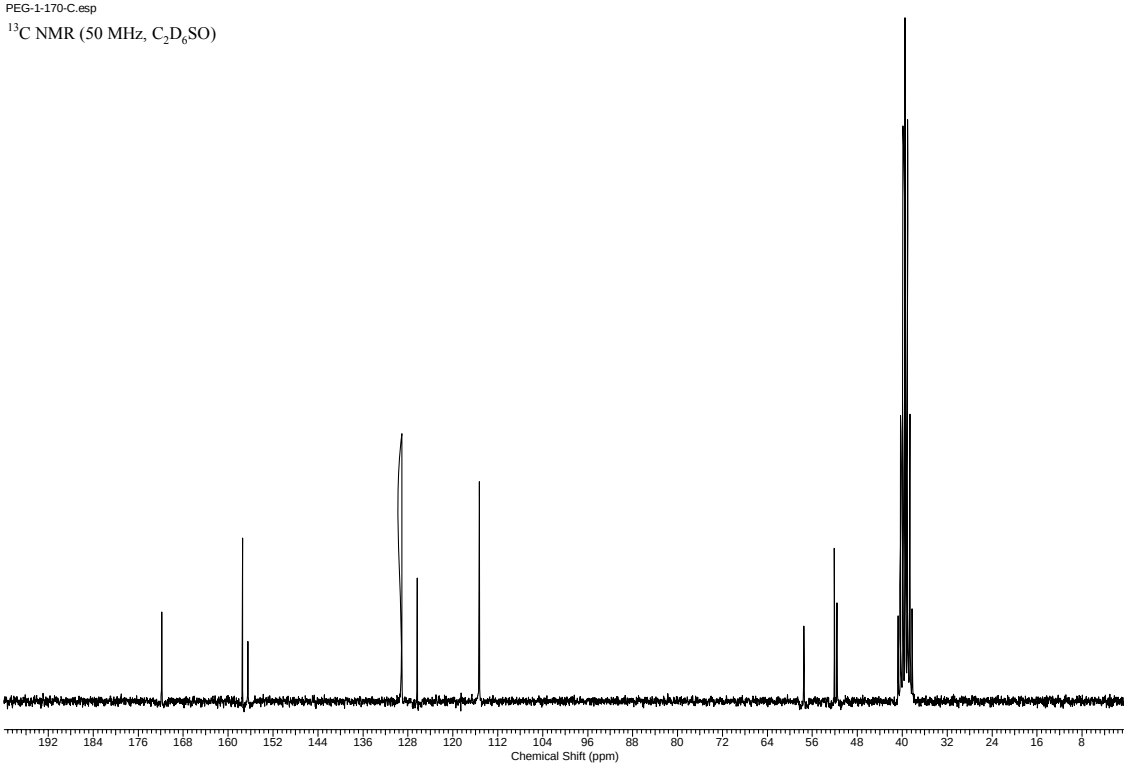
^{1}H NMR (200 MHz, C_2D_6SO)



152

PEG-1-170-C.esp

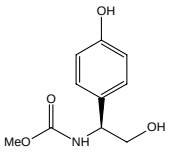
^{13}C NMR (50 MHz, C_2D_6SO)



(S)-Methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate 151

peg_3_005_H.esp

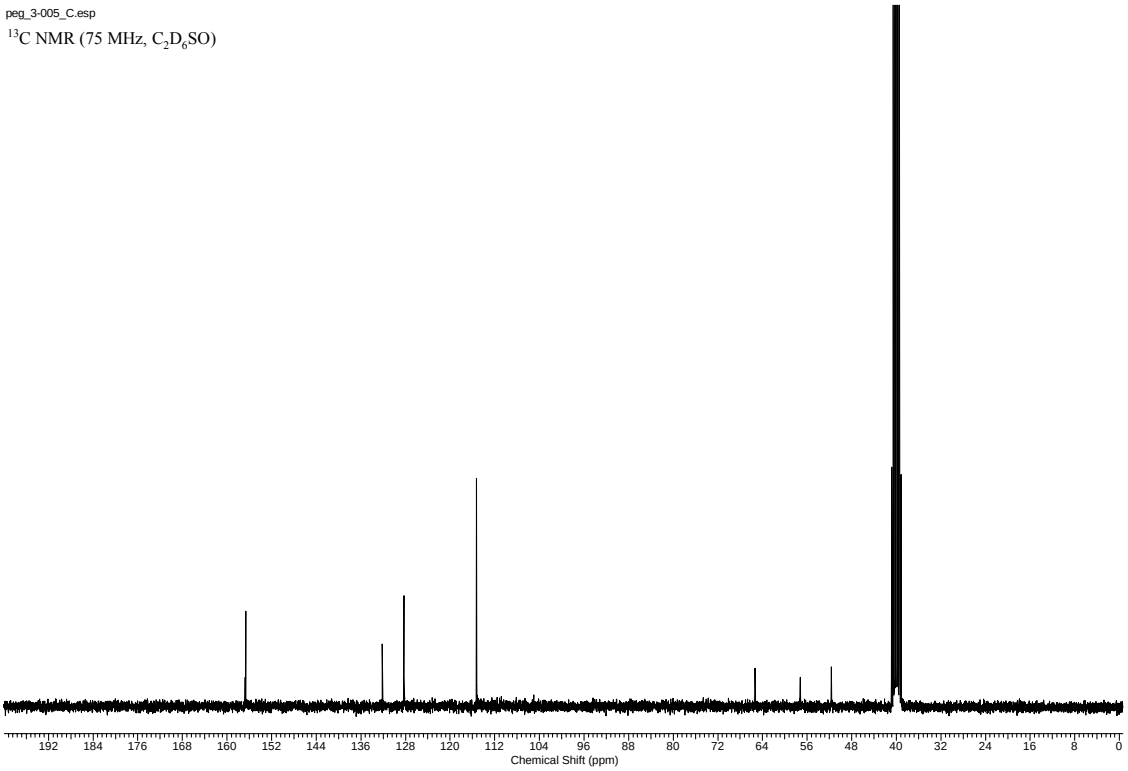
^{1}H NMR (300 MHz, C_2D_6SO)



151

peg_3-005_C.esp

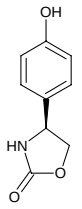
^{13}C NMR (75 MHz, C_2D_6SO)



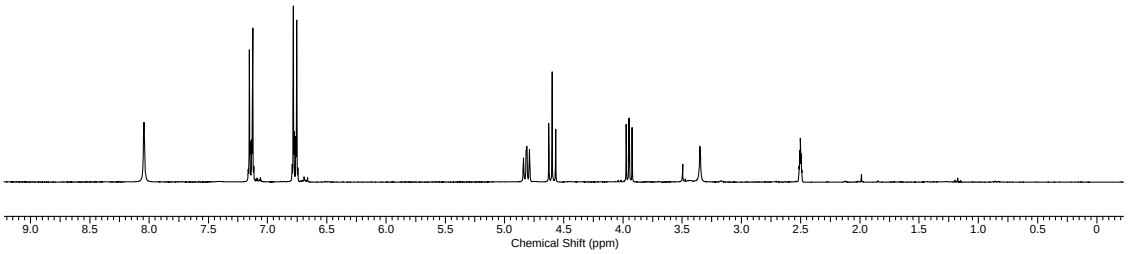
(S)-4-(4-Hydroxyphenyl)oxazolidin-2-one 153

R031 H.esp

^{1}H NMR (300 MHz, C_2D_6SO)

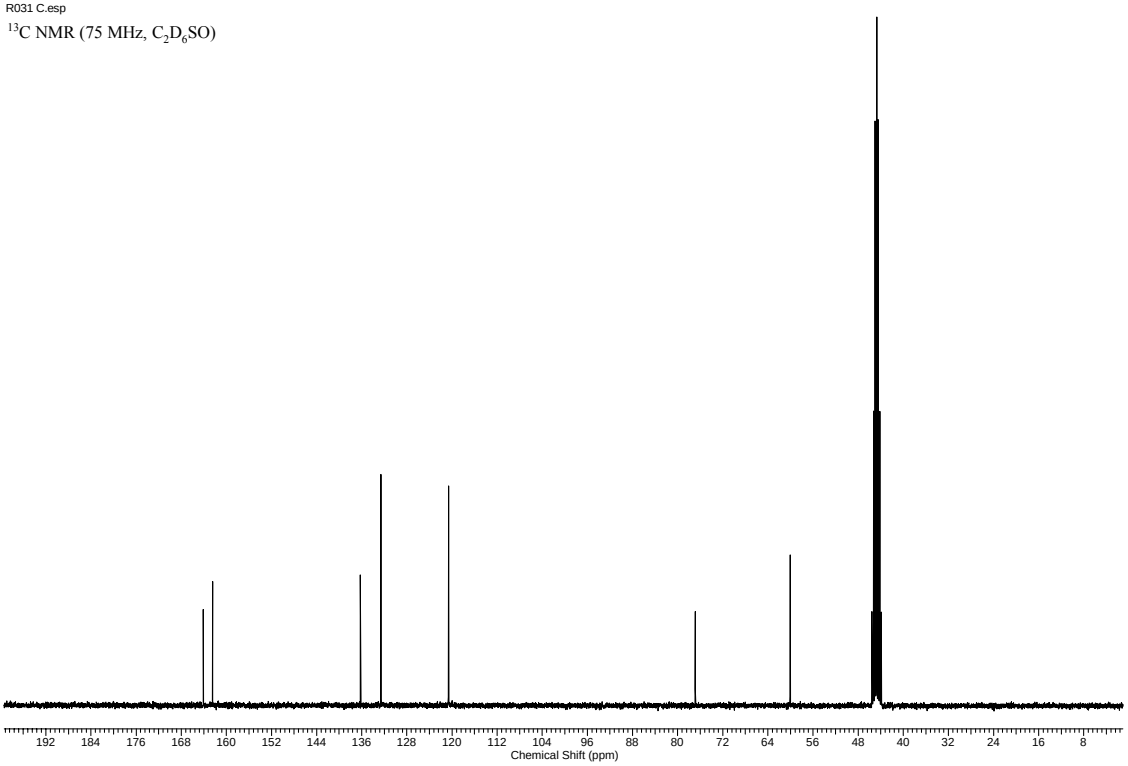


153



R031 C.esp

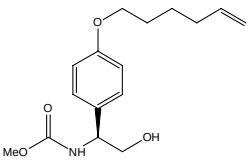
^{13}C NMR (75 MHz, C_2D_6SO)



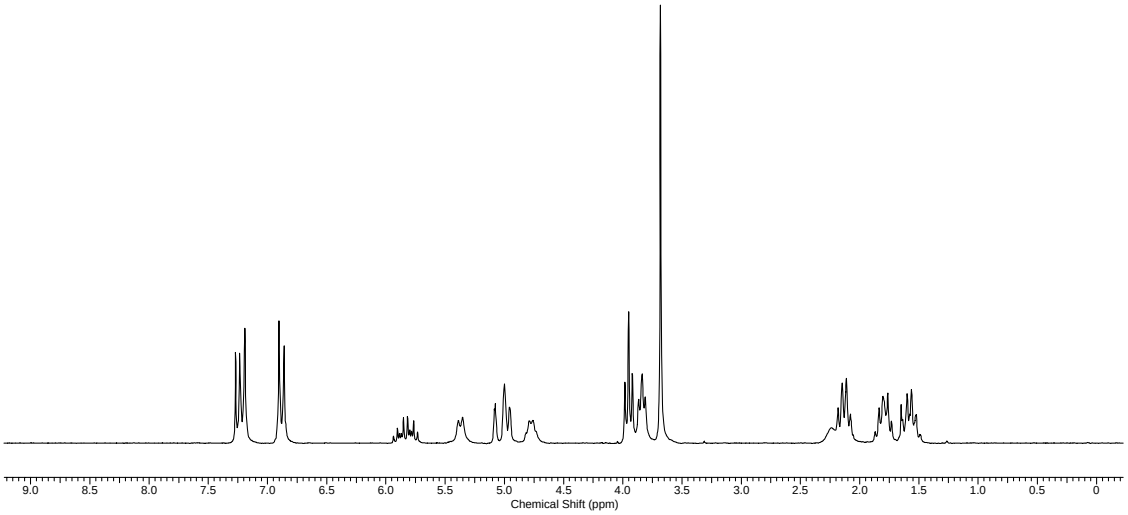
(S)-Methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate 144

PEG-1-020-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

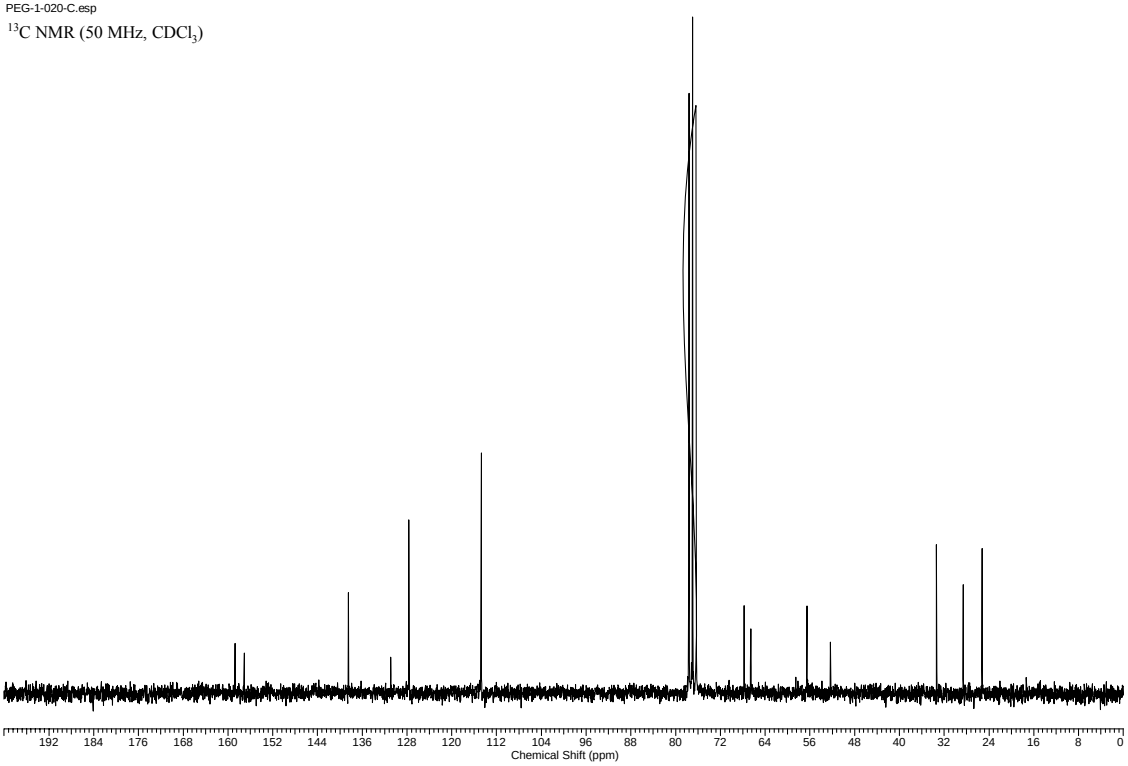


144



PEG-1-020-C.esp

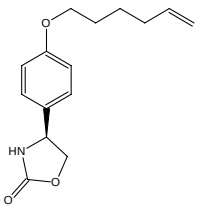
^{13}C NMR (50 MHz, $CDCl_3$)



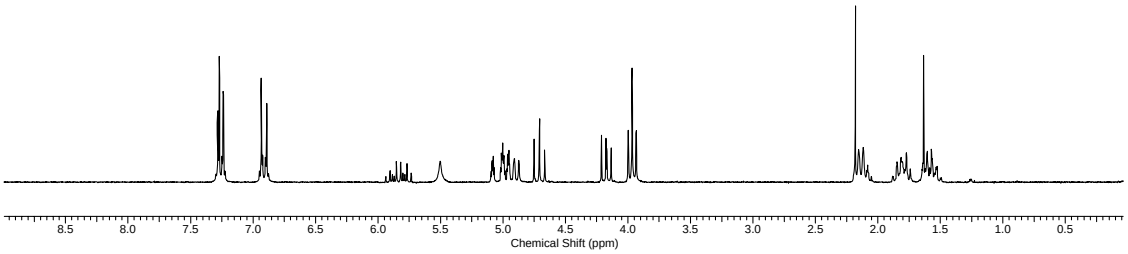
(S)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one 154

PEG--1-110A-H.ESP

^{1}H NMR (200 MHz, $CDCl_3$)

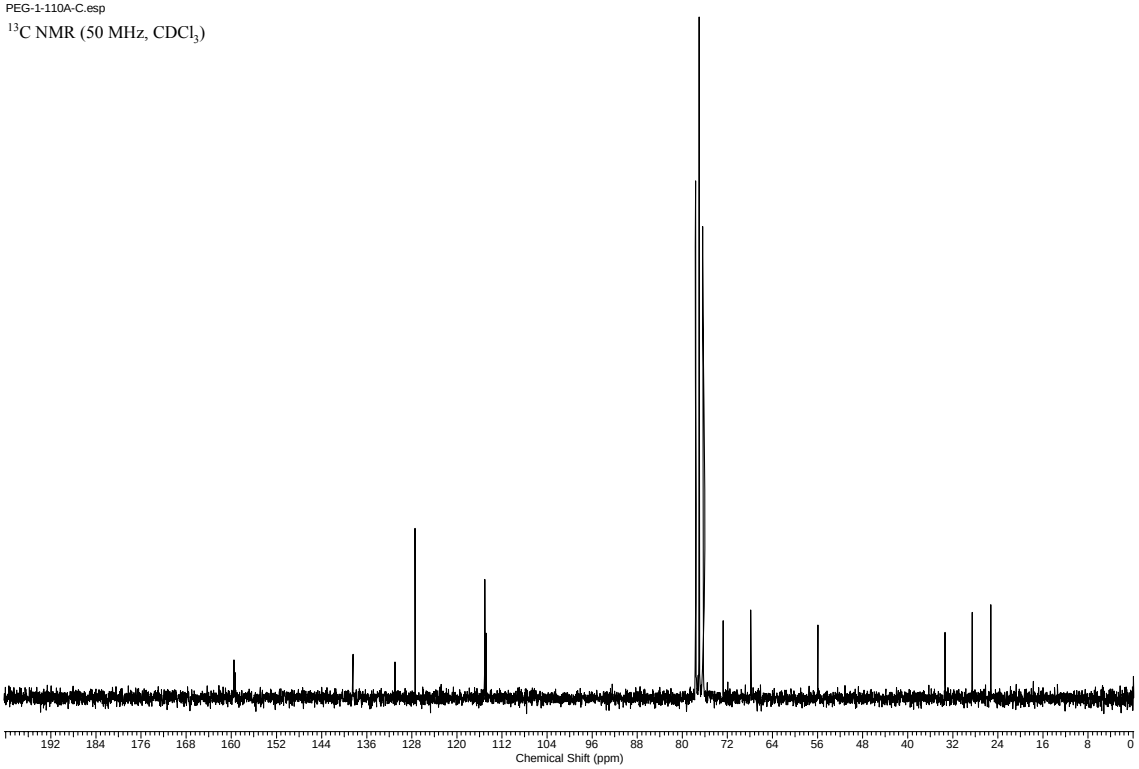


154



PEG-1-110A-C.esp

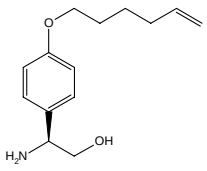
^{13}C NMR (50 MHz, $CDCl_3$)



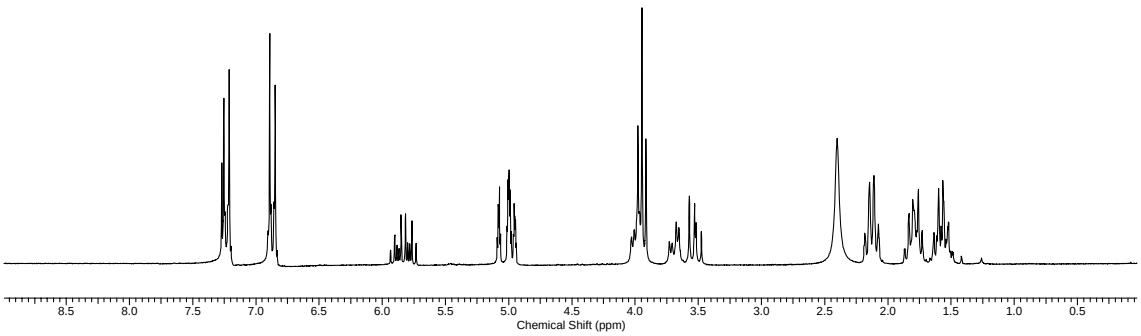
(S)-2-Amino-2-(4-(hex-5-enyloxy)phenyl)ethanol 142

PEG-1-021-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

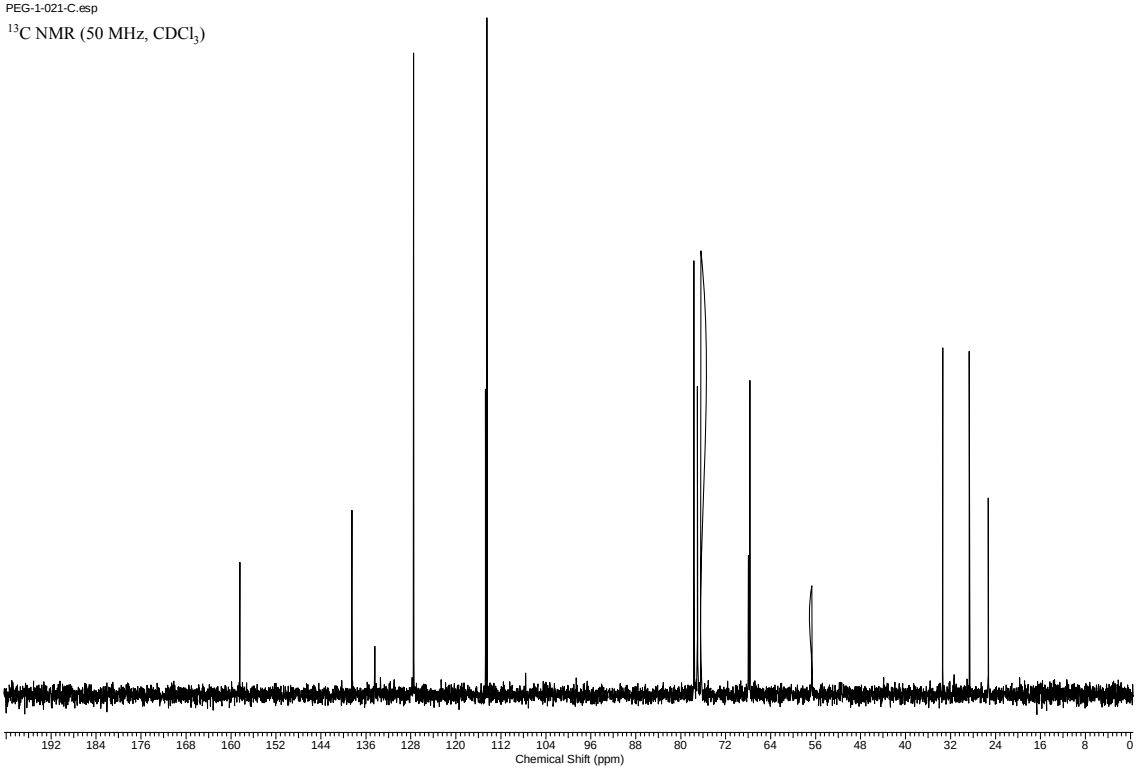


142



PEG-1-021-C.esp

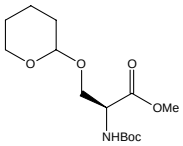
^{13}C NMR (50 MHz, $CDCl_3$)



*Methyl (2S)-2-(*tert*-butoxycarbonylamino)-3-(tetrahydro-2H-pyran-2-yloxy) propanoate 158*

PEG-1-023-H.esp

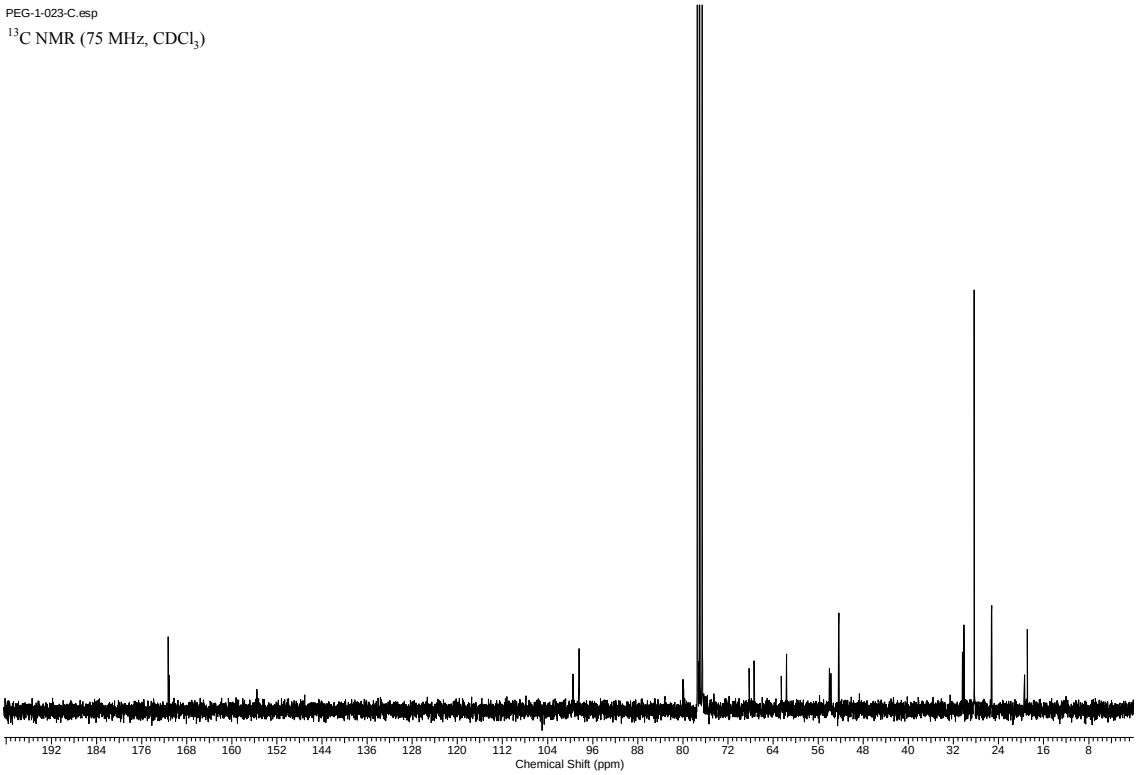
^{1}H NMR (300 MHz, $CDCl_3$)



158

PEG-1-023-C.esp

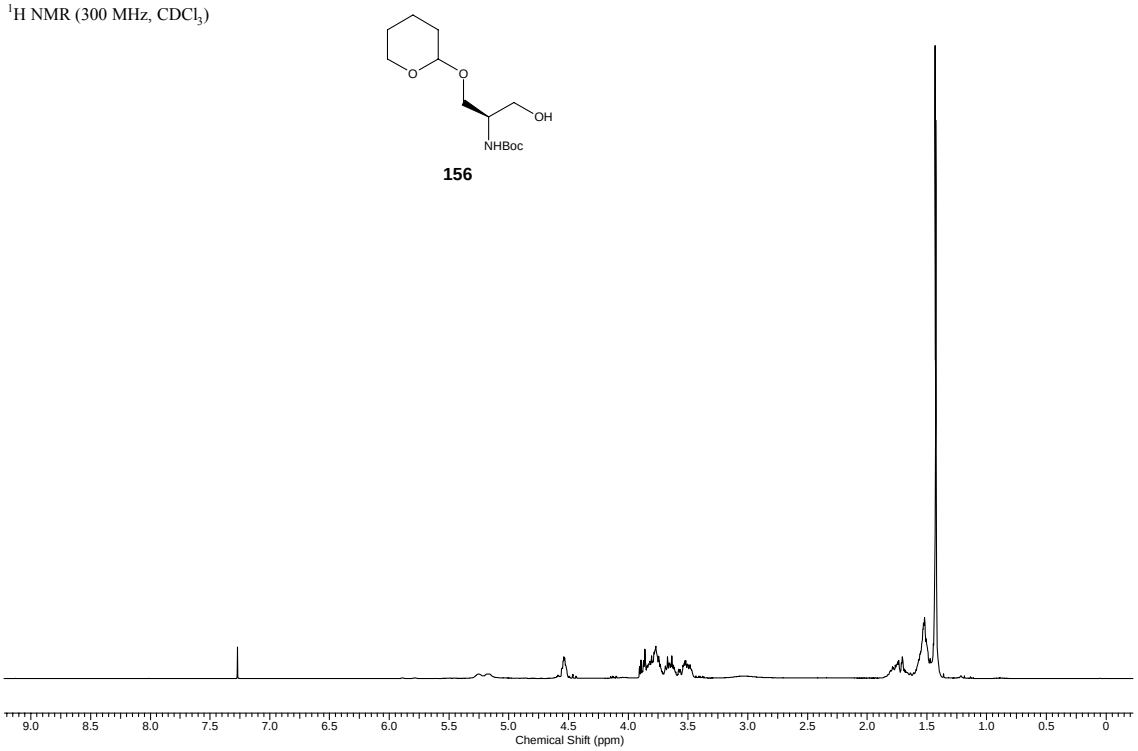
^{13}C NMR (75 MHz, $CDCl_3$)



tert-*Butyl (2*R*)-1-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate 156*

PEG-1-101-H.esp

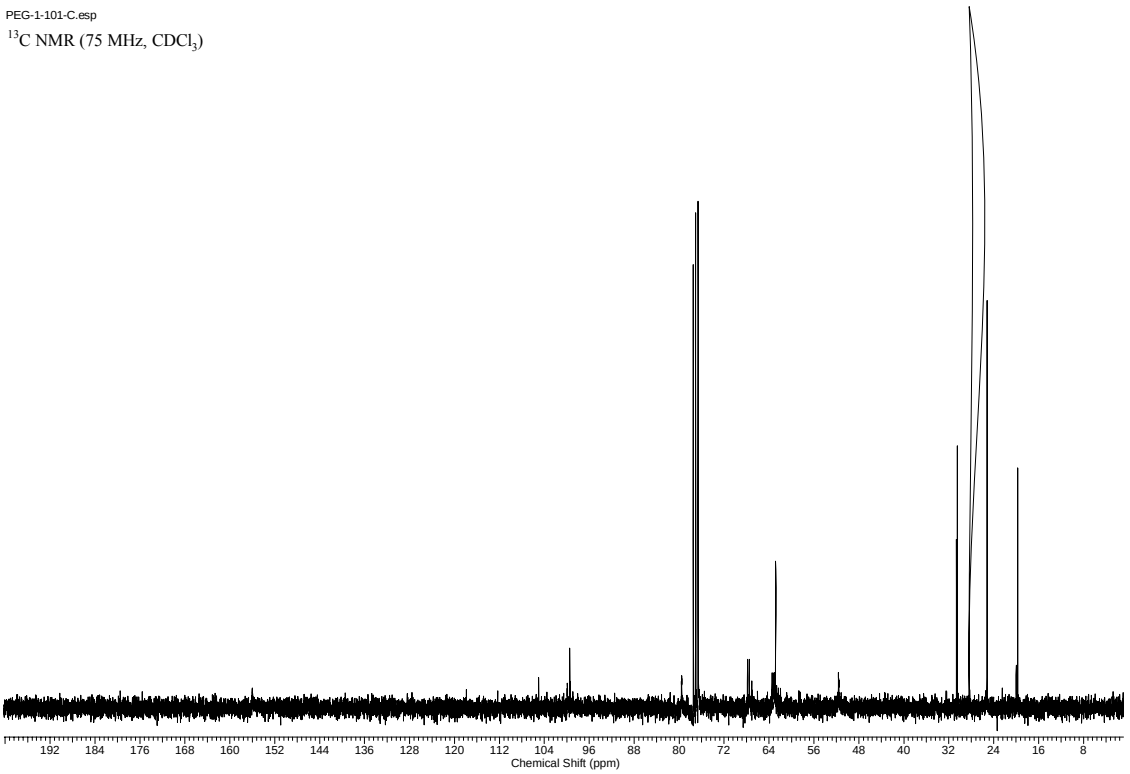
^{1}H NMR (300 MHz, $CDCl_3$)



156

PEG-1-101-C.esp

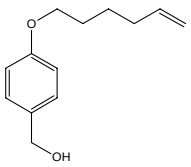
^{13}C NMR (75 MHz, $CDCl_3$)



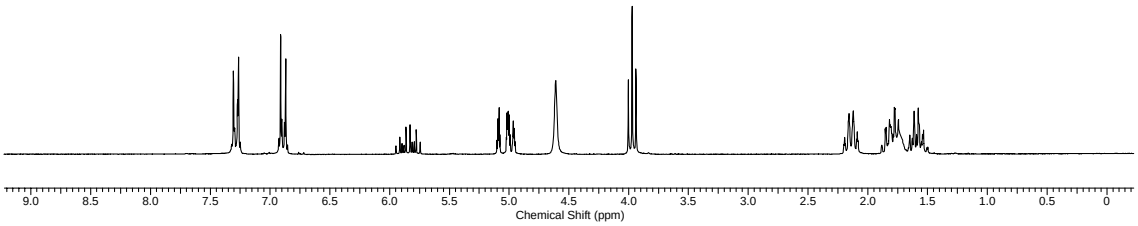
(4-(Hex-5-enyloxy)phenyl)methanol 161

PEG-1-011-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

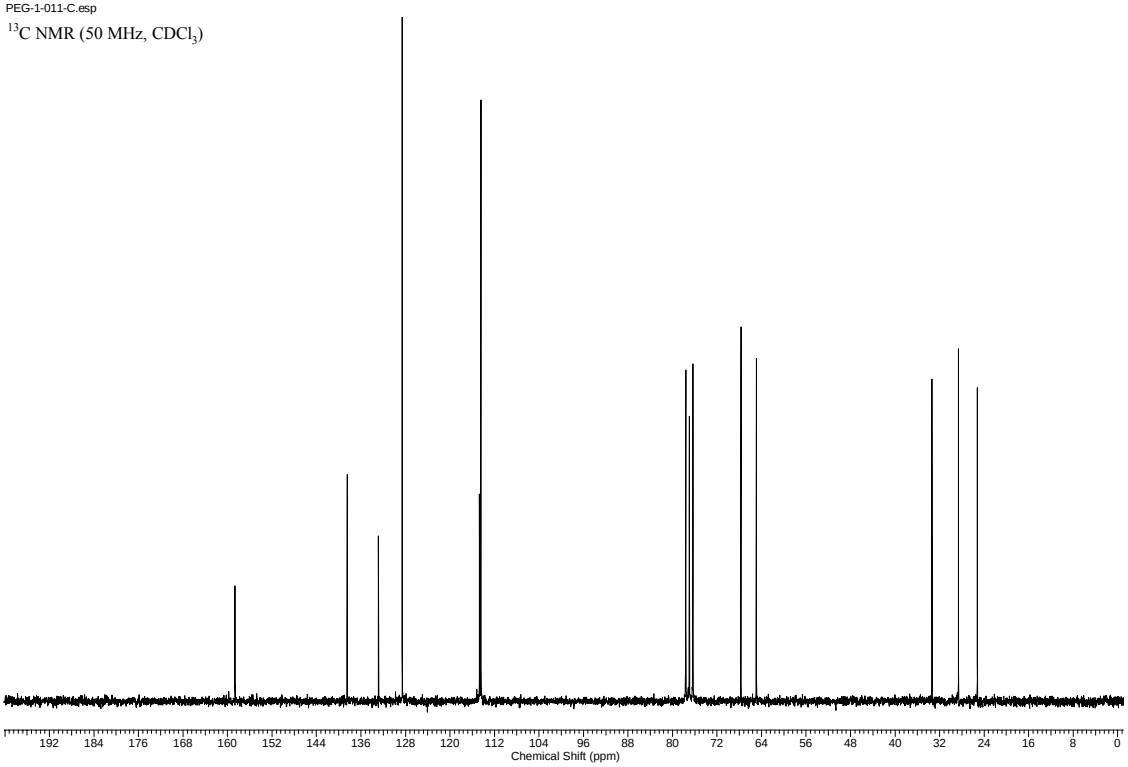


161



PEG-1-011-C.esp

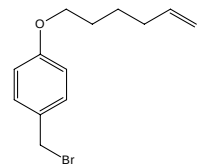
^{13}C NMR (50 MHz, $CDCl_3$)



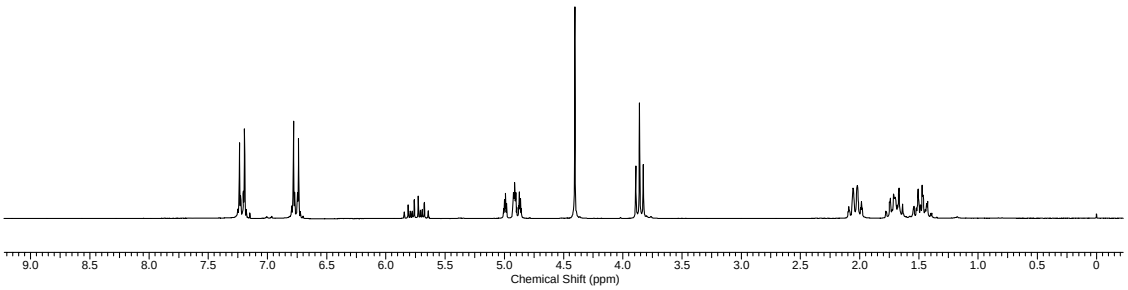
1-(Bromomethyl)-4-(hex-5-enyloxy)benzene 157

PEG-1-017-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

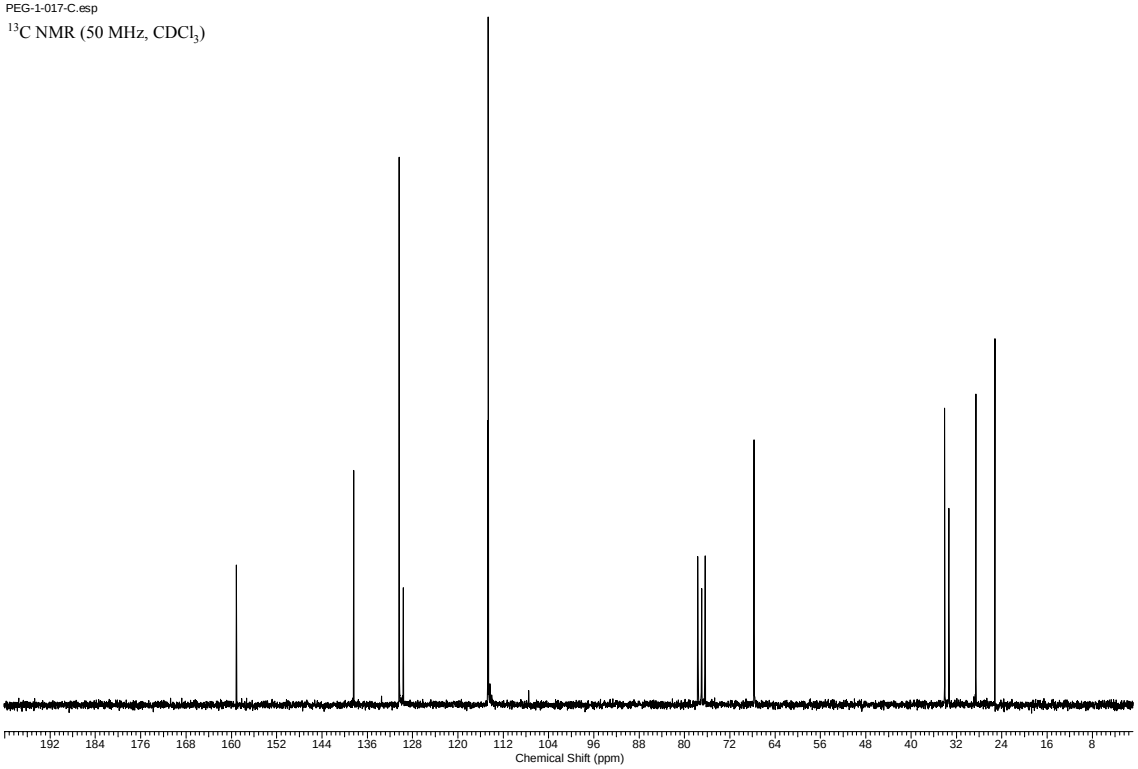


157



PEG-1-017-C.esp

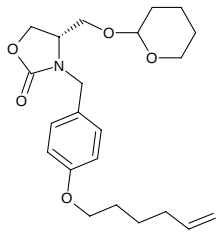
^{13}C NMR (50 MHz, $CDCl_3$)



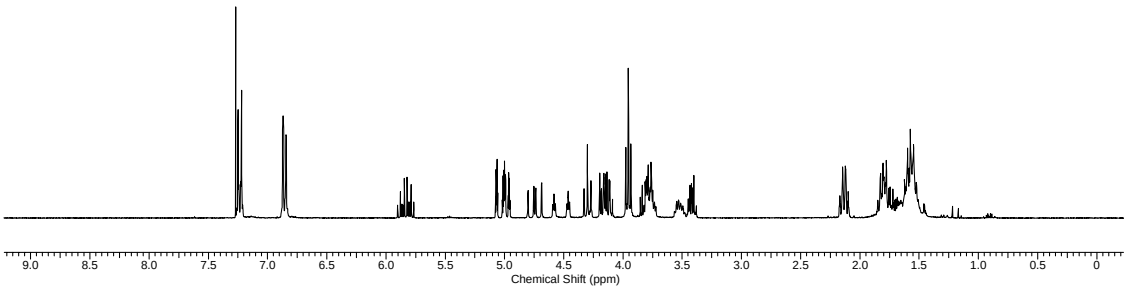
(4S)-3-(4-(Hex-5-enyloxy)benzyl)-4-((tetrahydro-2H-pyran-2-yloxy)methyl)oxazolidin-2-one 162

PEG-1-088-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

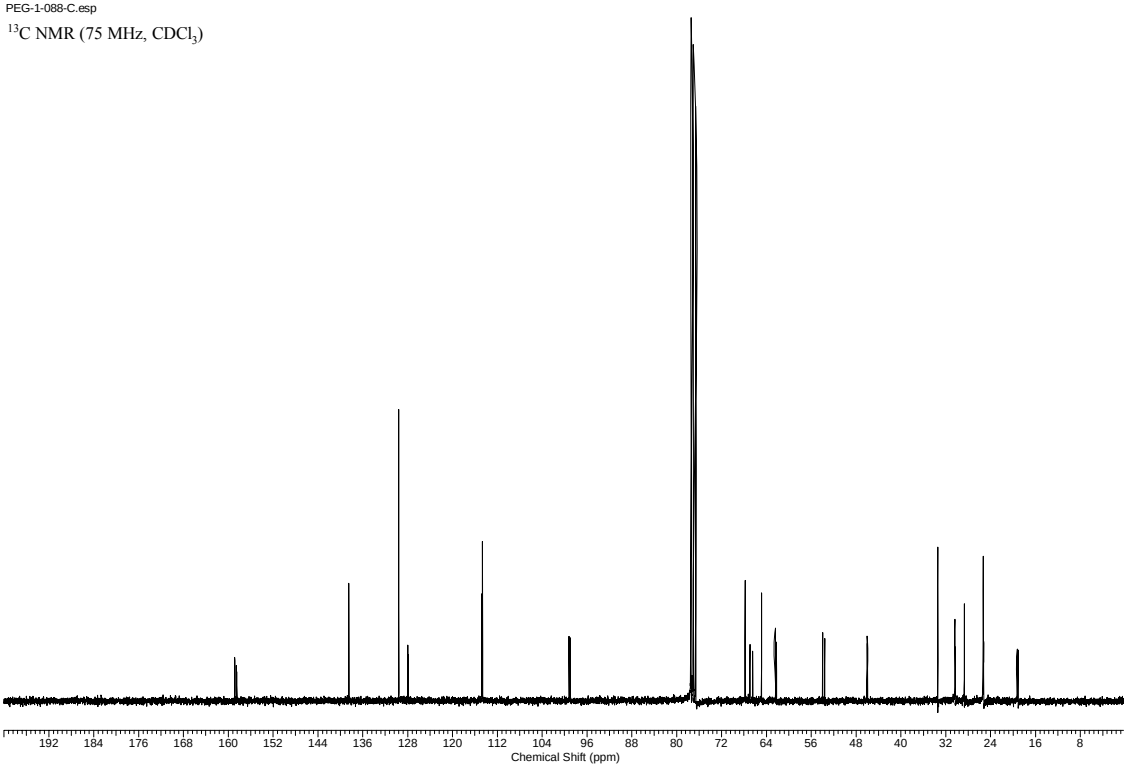


162



PEG-1-088-C.esp

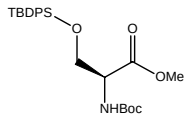
^{13}C NMR (75 MHz, $CDCl_3$)



*(S)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propanoate 163*

1135 H.esp

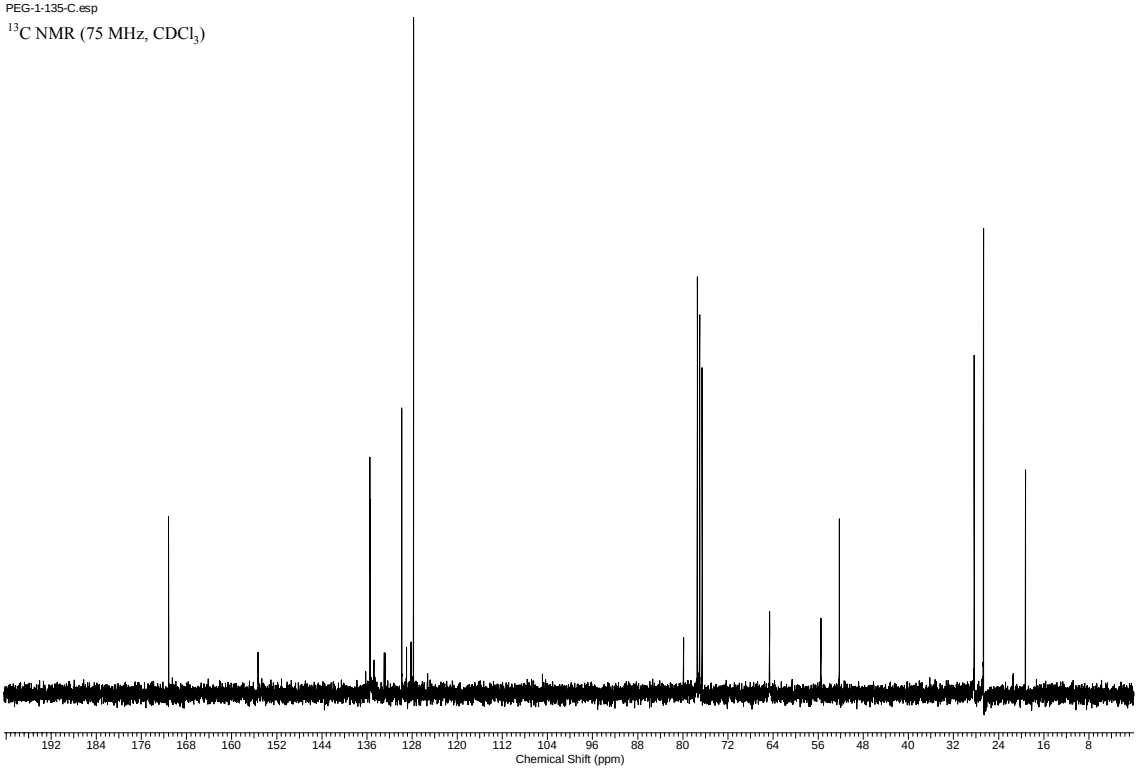
^{1}H NMR (300 MHz, $CDCl_3$)



163

PEG-1-135-C.esp

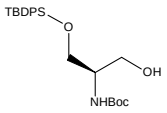
^{13}C NMR (75 MHz, $CDCl_3$)



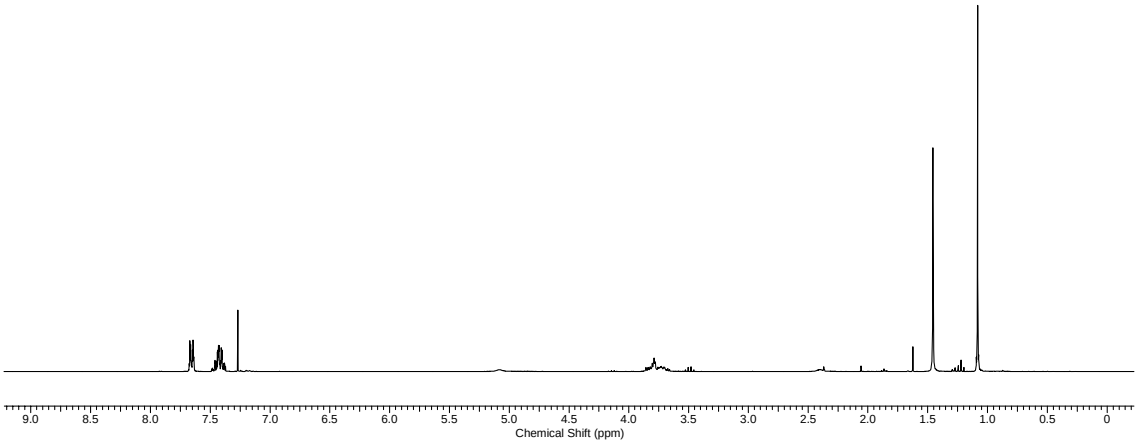
*(*R*)*-tert-*Butyl 1-(*tert-*butyldiphenylsilyloxy)-3-hydroxypropan-2-ylcarbamate 164*

PEG-1-140-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

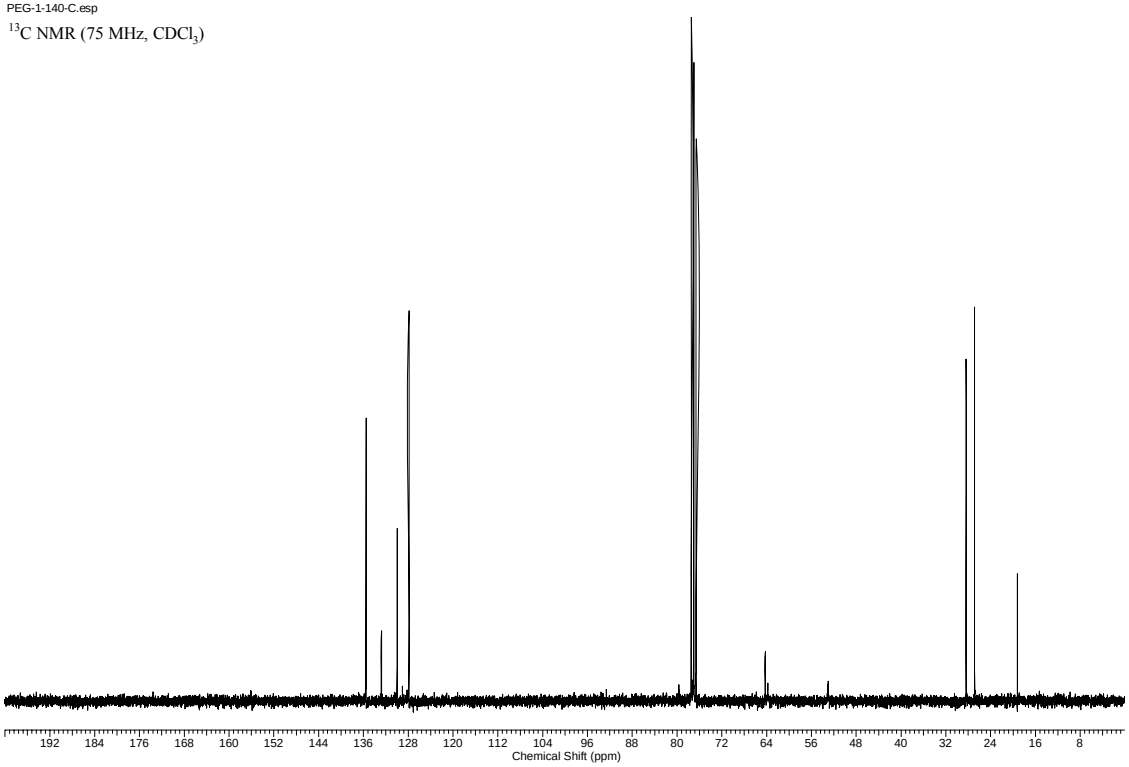


164



PEG-1-140-C.esp

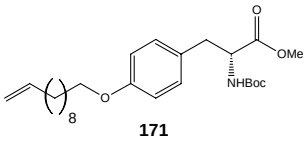
^{13}C NMR (75 MHz, $CDCl_3$)



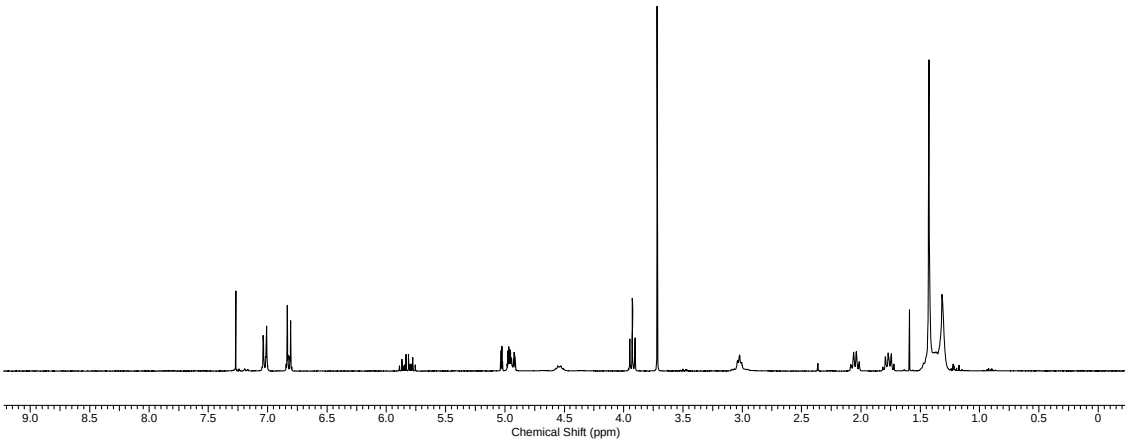
*(***R***)-Methyl 2-(***tert***-butoxycarbonylamino)-3-(4-(undec-10-enyloxy)phenyl)propanoate 171*

PEG-1-148A-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

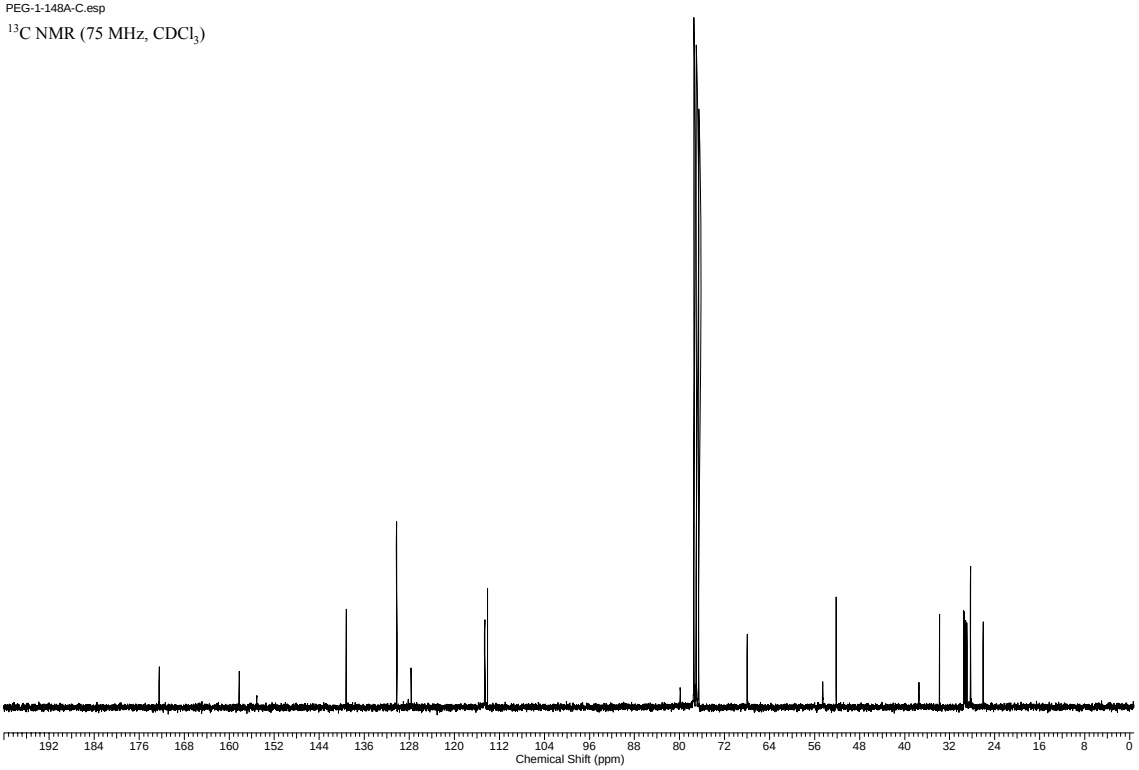


171



PEG-1-148A-C.esp

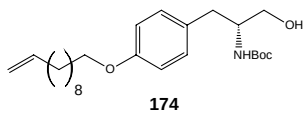
^{13}C NMR (75 MHz, $CDCl_3$)



*(*R*)*-tert-*Butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-ylcarbamate 174*

PEG-1-149B-H.esp

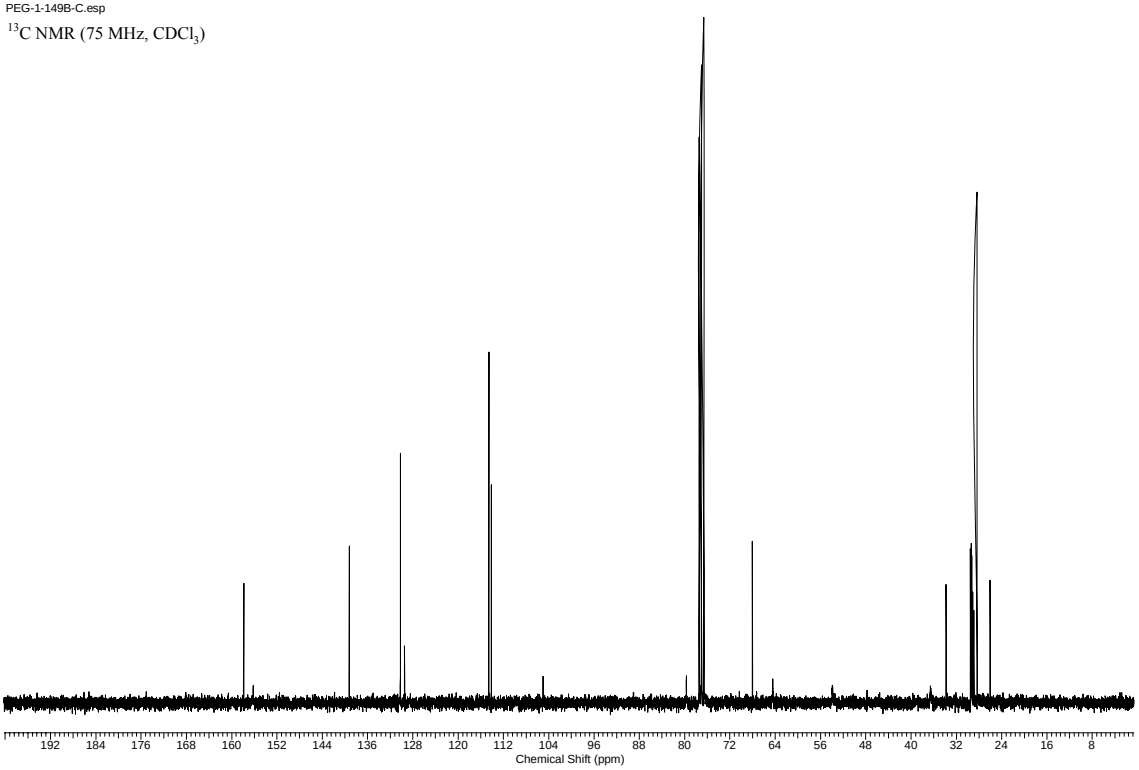
^{1}H NMR (300 MHz, $CDCl_3$)



174

PEG-1-149B-C.esp

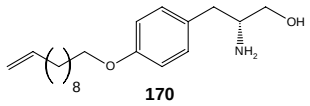
^{13}C NMR (75 MHz, $CDCl_3$)



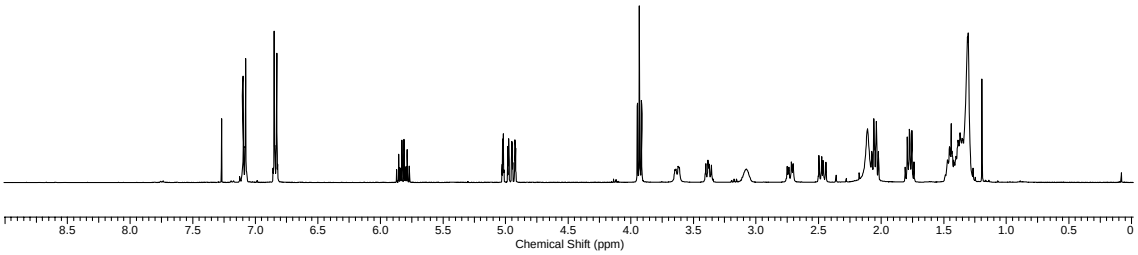
(R)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol 170

PEG-1-153-H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

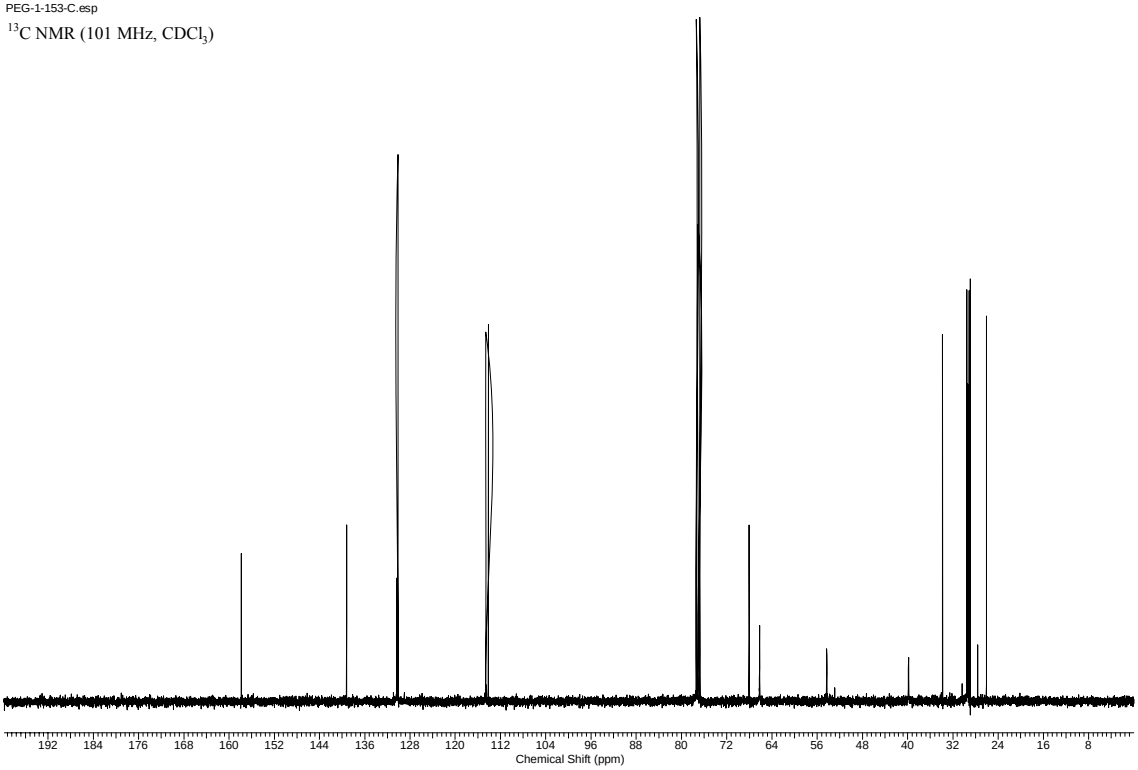


170



PEG-1-153-C.esp

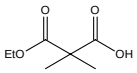
^{13}C NMR (101 MHz, $CDCl_3$)



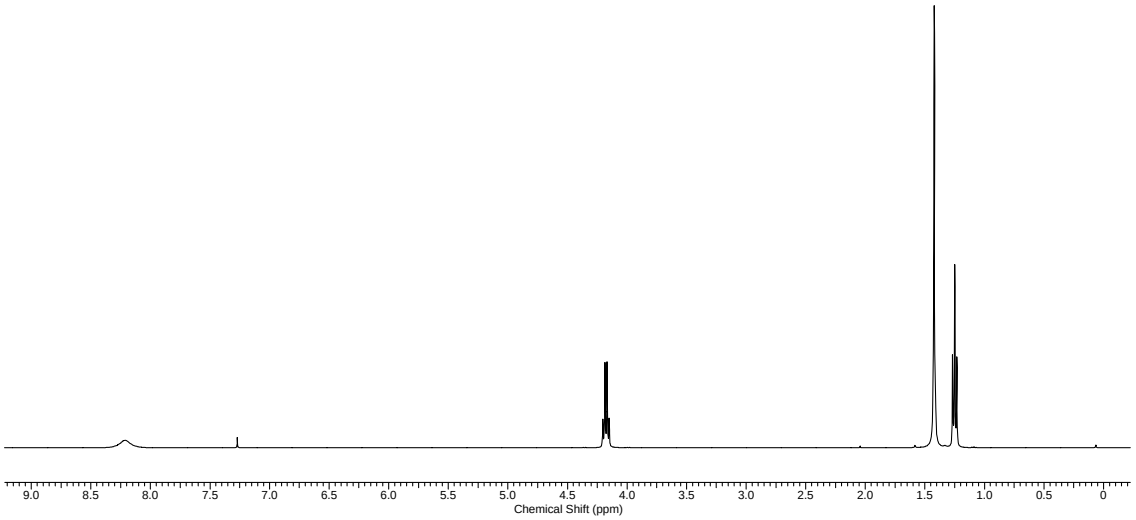
3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid 141

PEG-1-002-H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

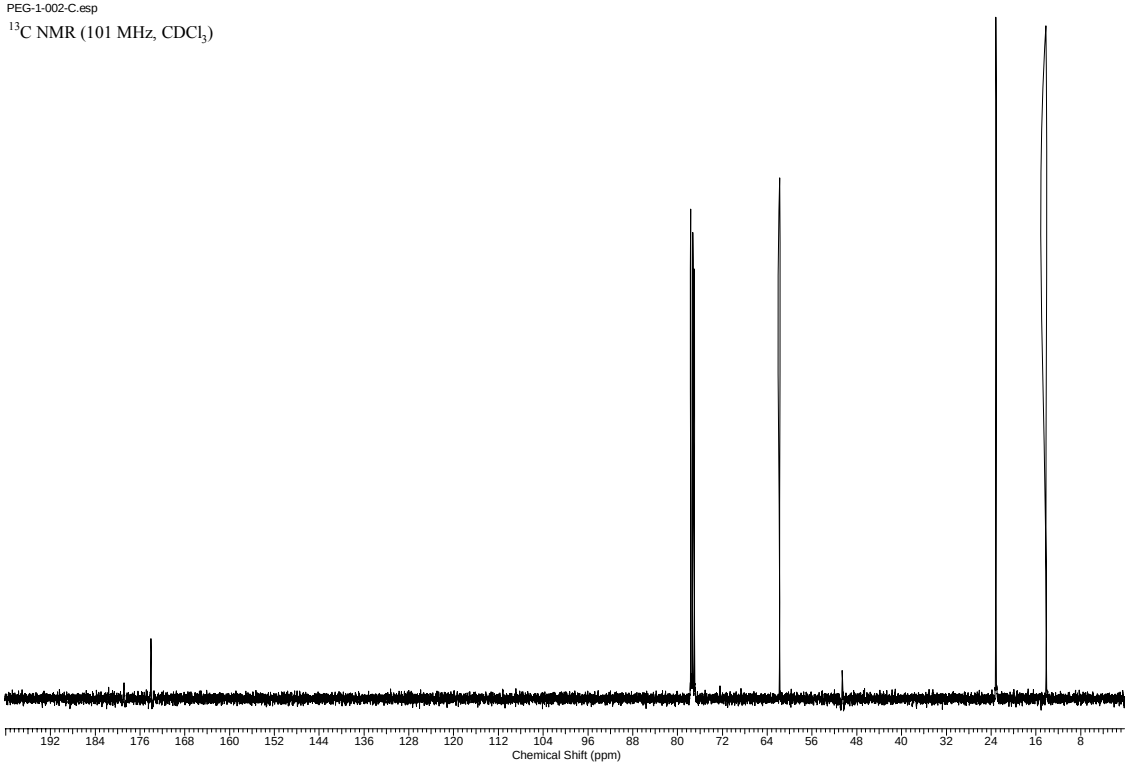


141



PEG-1-002-C.esp

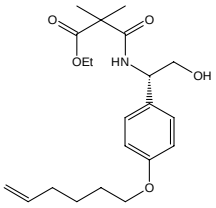
^{13}C NMR (101 MHz, $CDCl_3$)



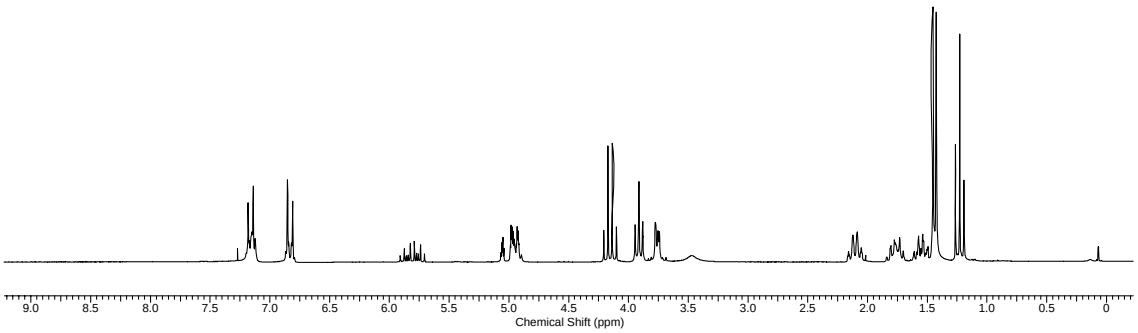
(S)-Ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoate 176

PEG-1-030-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

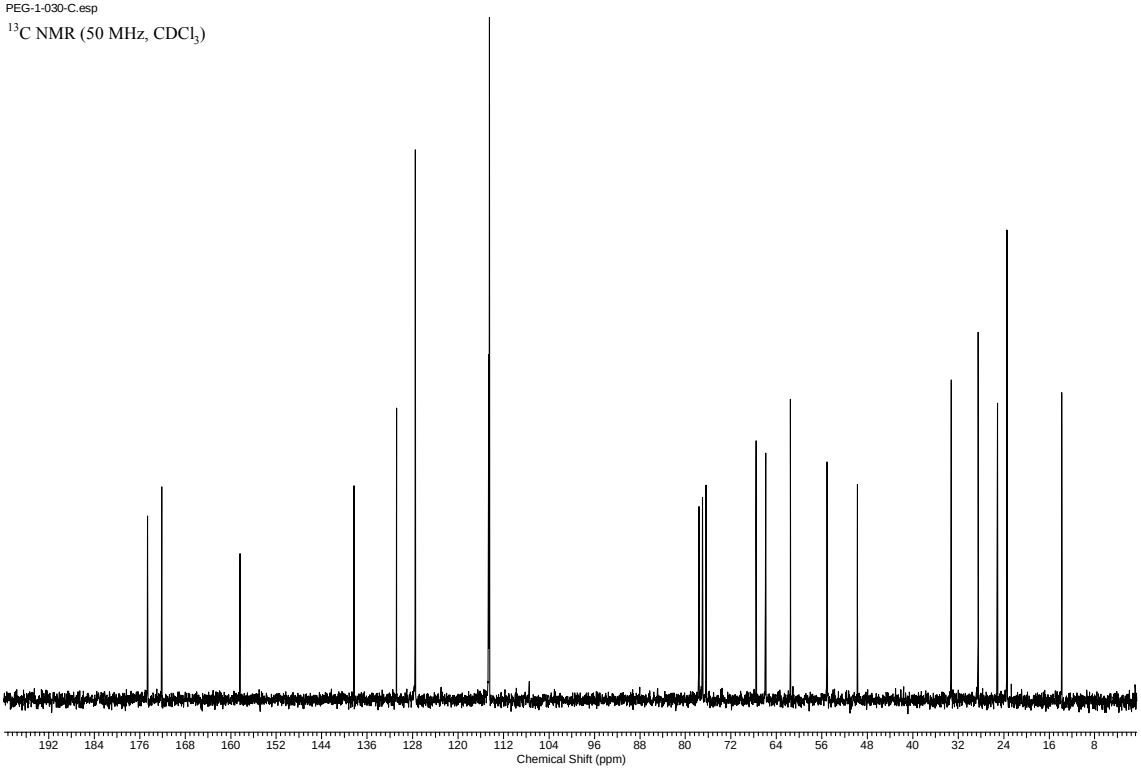


176



PEG-1-030-C.esp

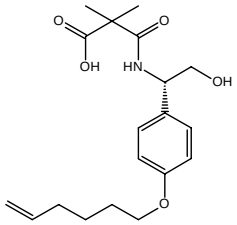
^{13}C NMR (50 MHz, $CDCl_3$)



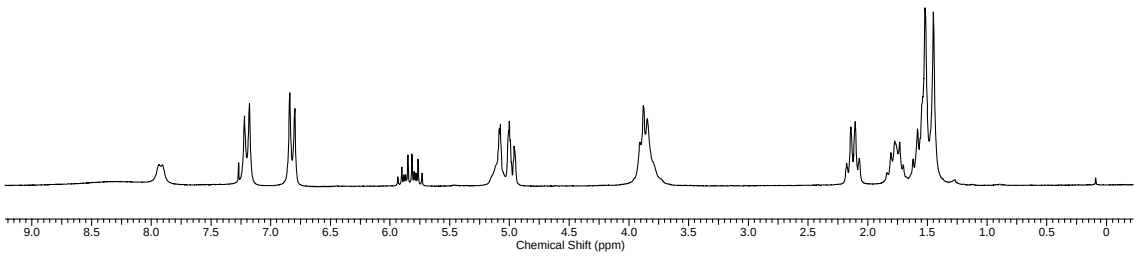
(S)-3-(1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxo propanoic acid 177

PEG-1-036-H.esp

^{1}H NMR (200 MHz, $CDCl_3$)

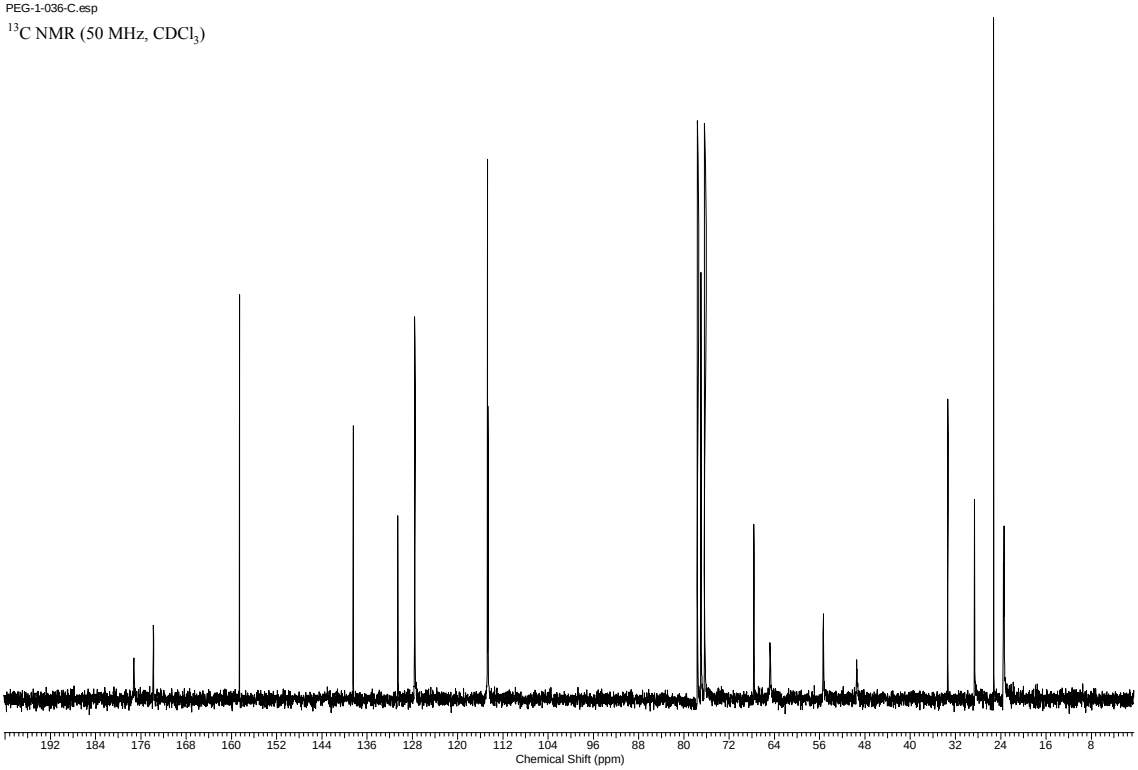


177



PEG-1-036-C.esp

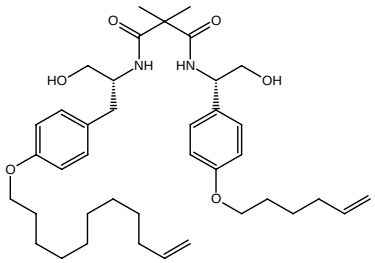
^{13}C NMR (50 MHz, $CDCl_3$)



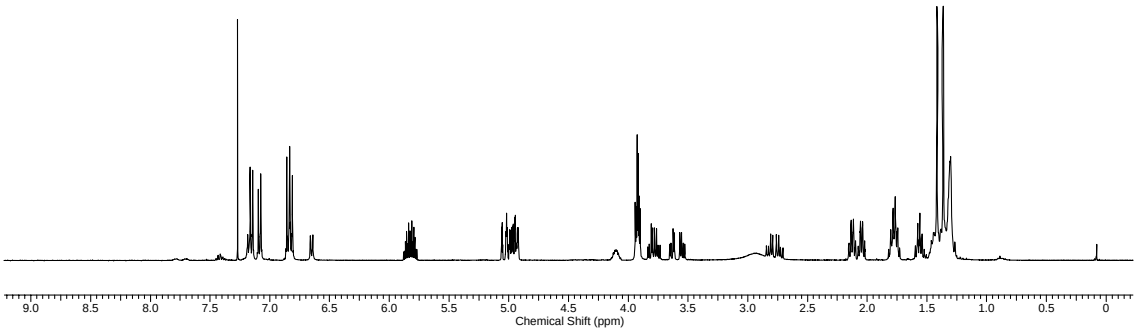
N^{1}-((S)-1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethyl)-N^{3}-((R)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide 169

PEG-1-152C-H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

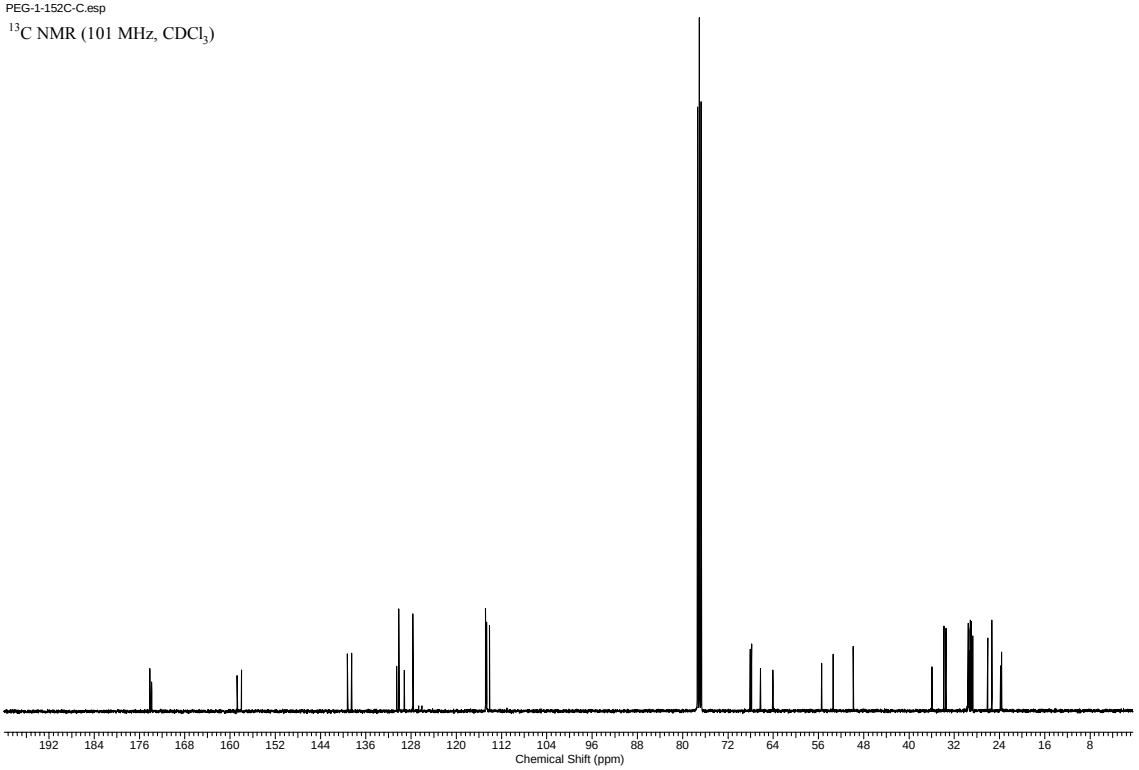


169



PEG-1-152C-C.esp

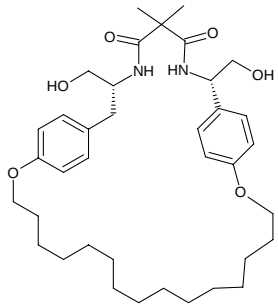
^{13}C NMR (101 MHz, $CDCl_3$)



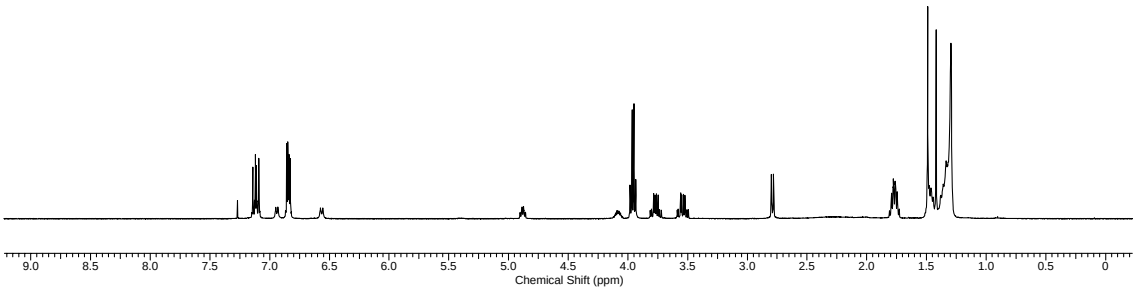
Macrocycle 168

PEG-3_075-H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

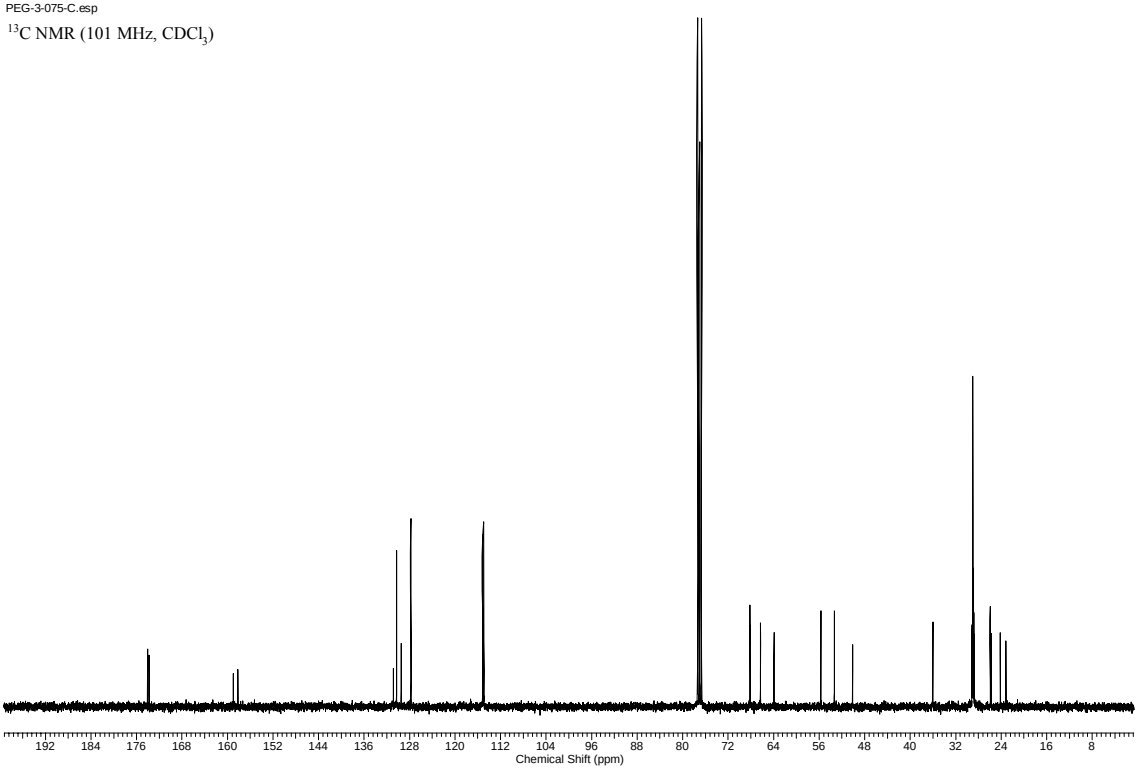


168



PEG-3-075-C.esp

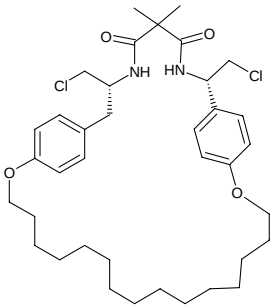
^{13}C NMR (101 MHz, $CDCl_3$)



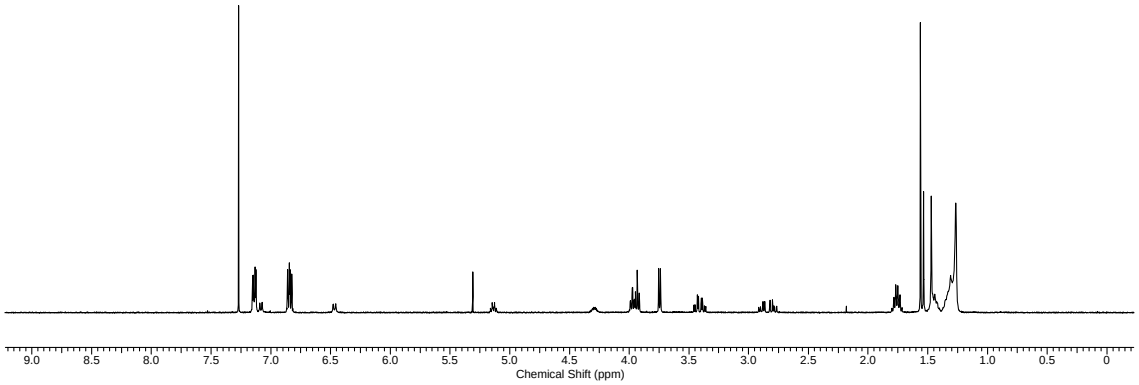
Macrocycle 178

PEG-3-076-H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

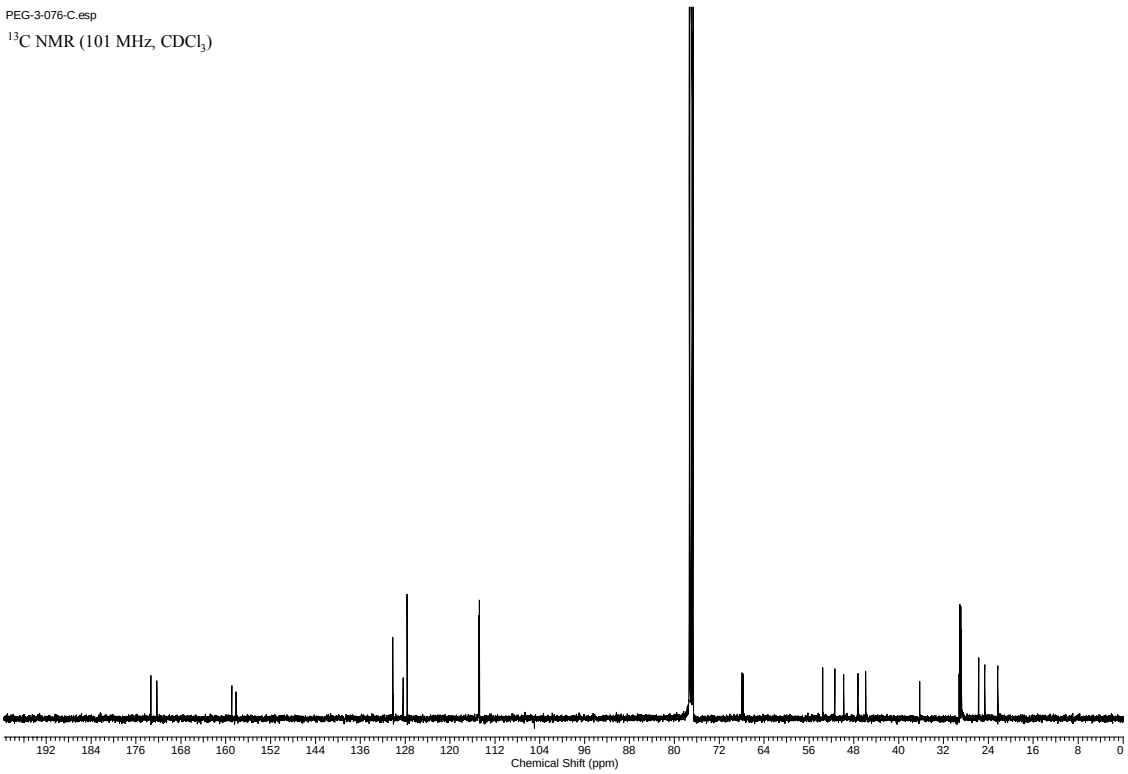


178



PEG-3-076-C.esp

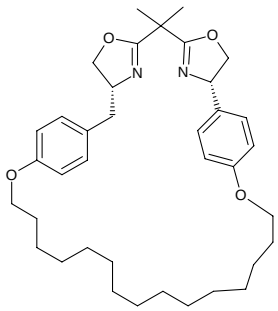
^{13}C NMR (101 MHz, $CDCl_3$)



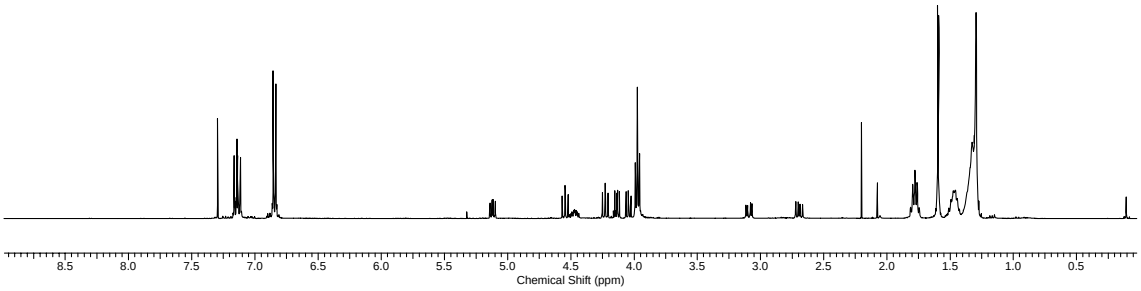
Macrocycle 167

3140H.esp

^{1}H NMR (400 MHz, $CDCl_3$)

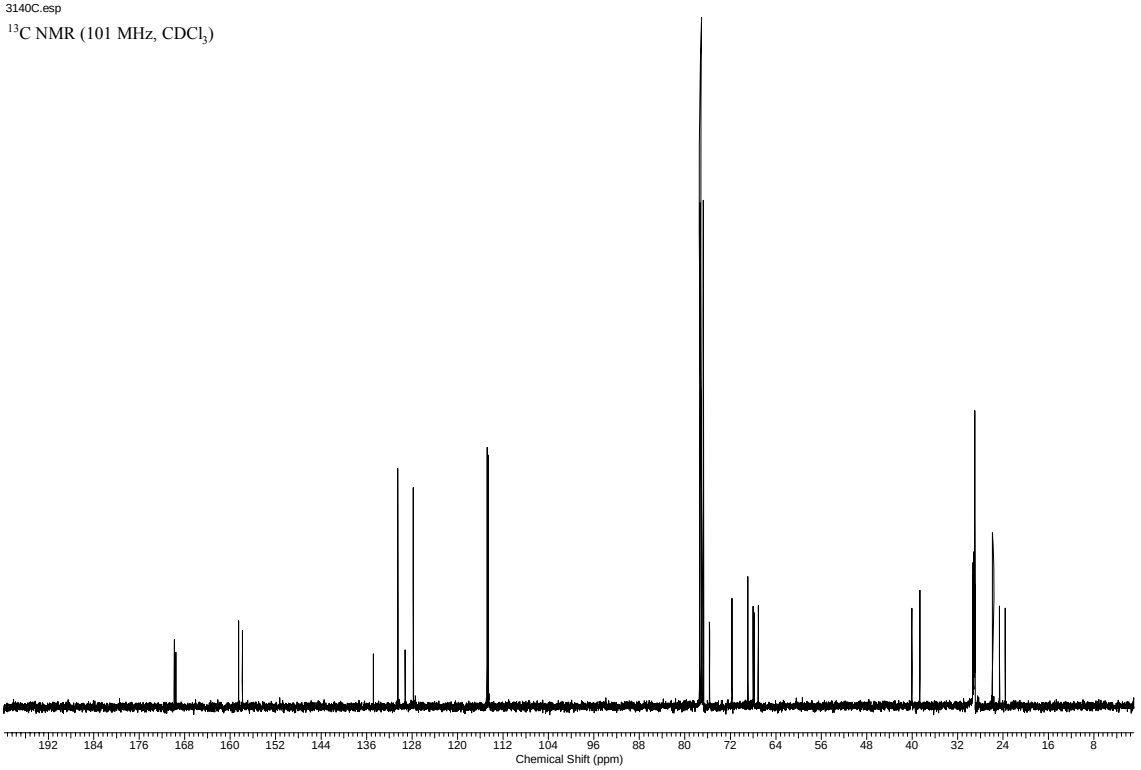


167



3140C.esp

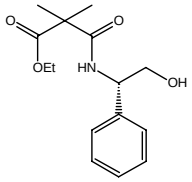
^{13}C NMR (101 MHz, $CDCl_3$)



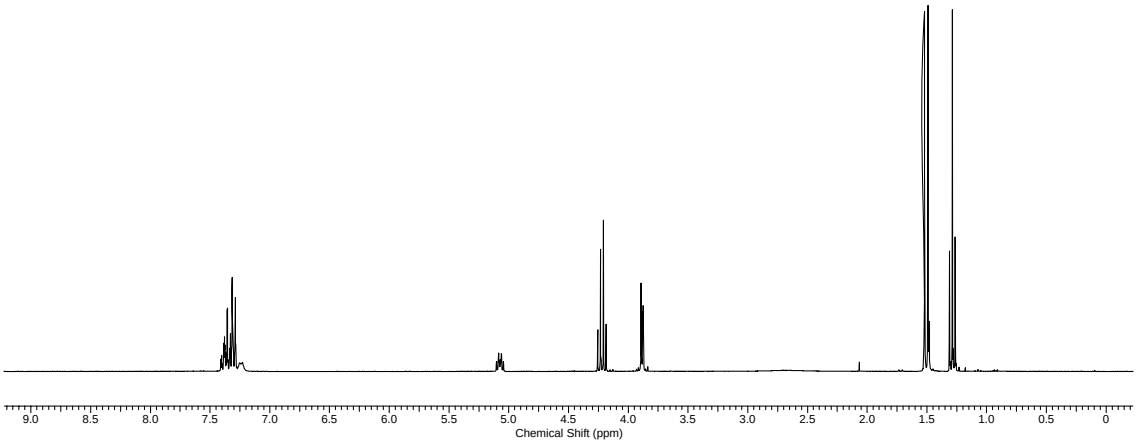
(S)-Ethyl 3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoate 183

PEG-3-090-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

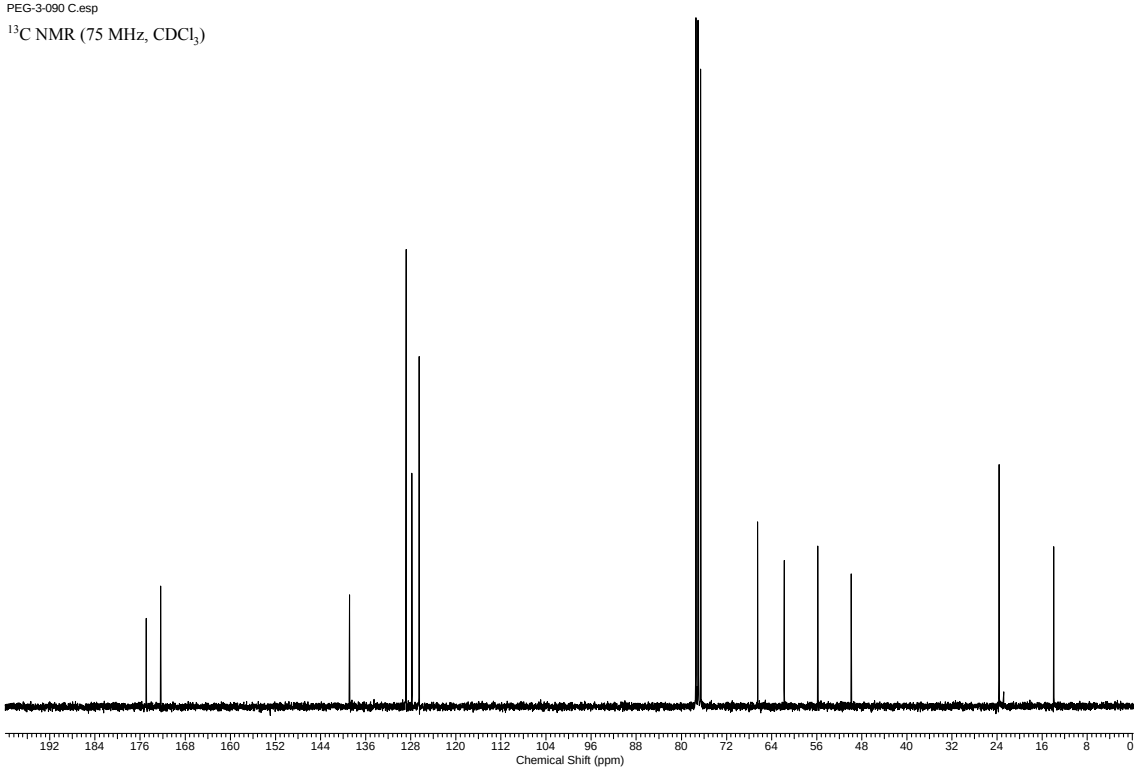


183



PEG-3-090 C.esp

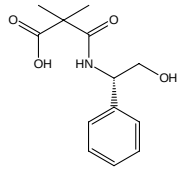
^{13}C NMR (75 MHz, $CDCl_3$)



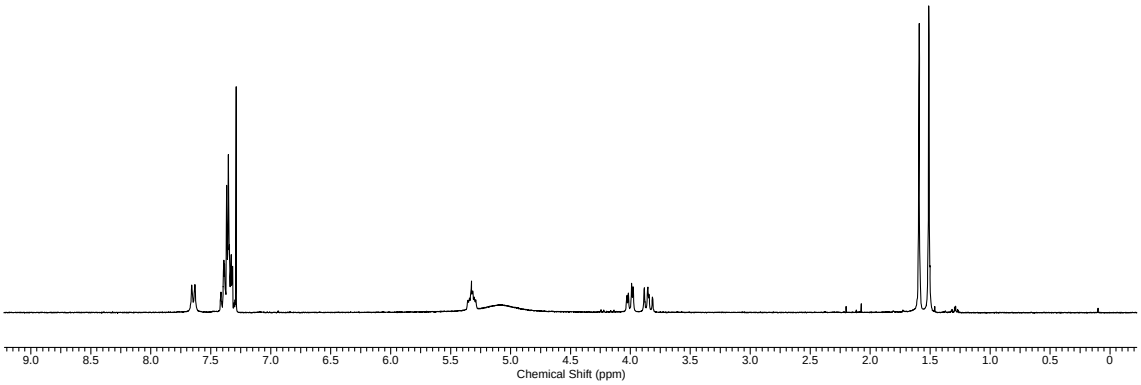
(S)-3-(2-Hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid 184

3105H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

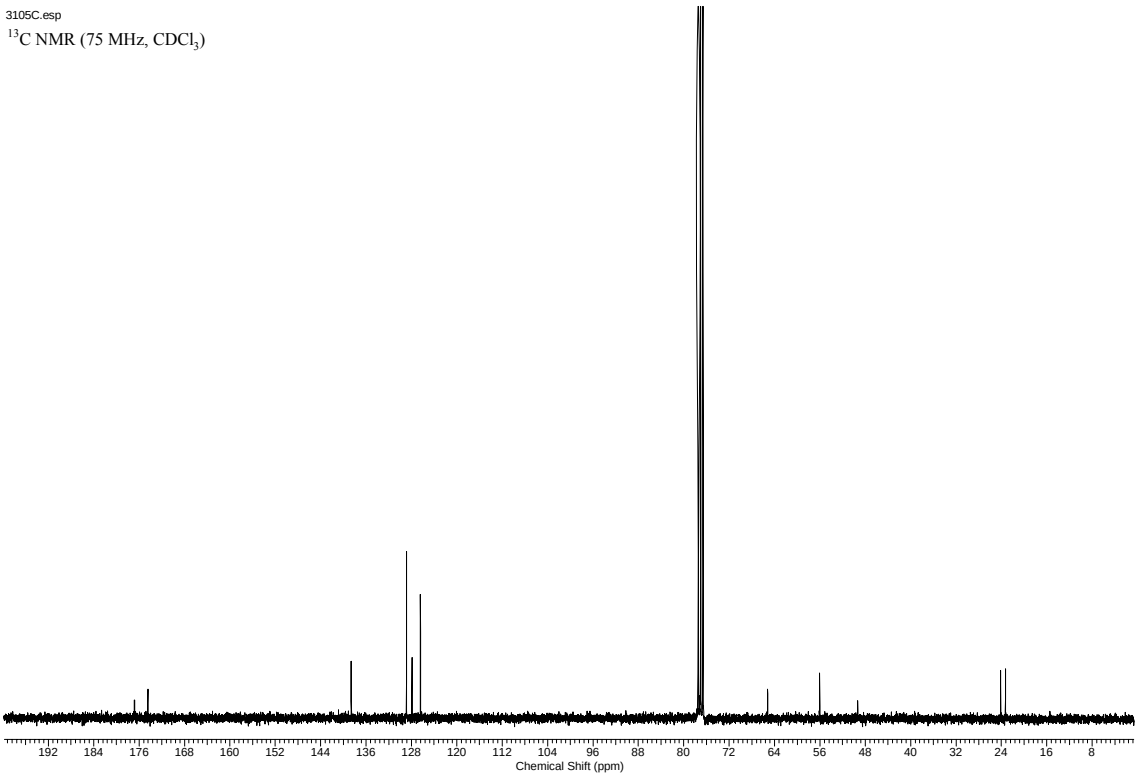


184



3105C.esp

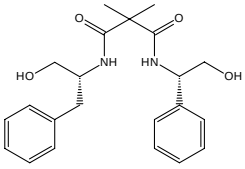
^{13}C NMR (75 MHz, $CDCl_3$)



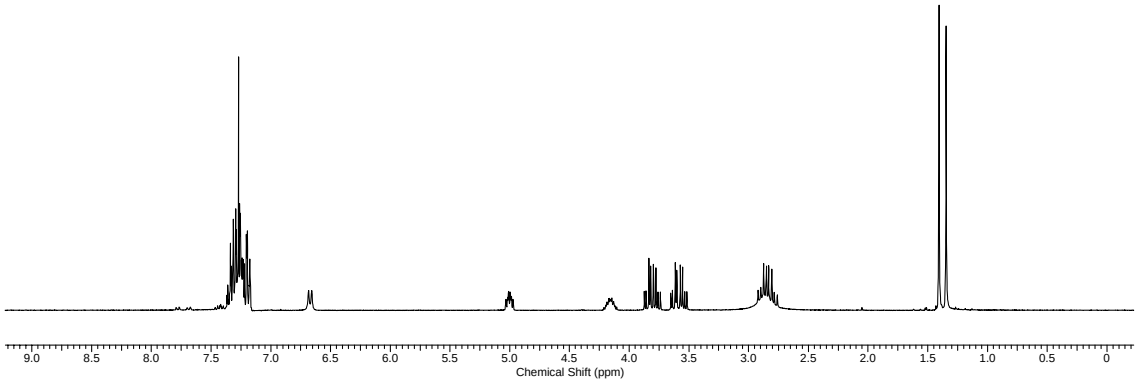
N^1-((S)-2-Hydroxy-1-phenylethyl)-N^3-((R)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide 186

PEG-3-093-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

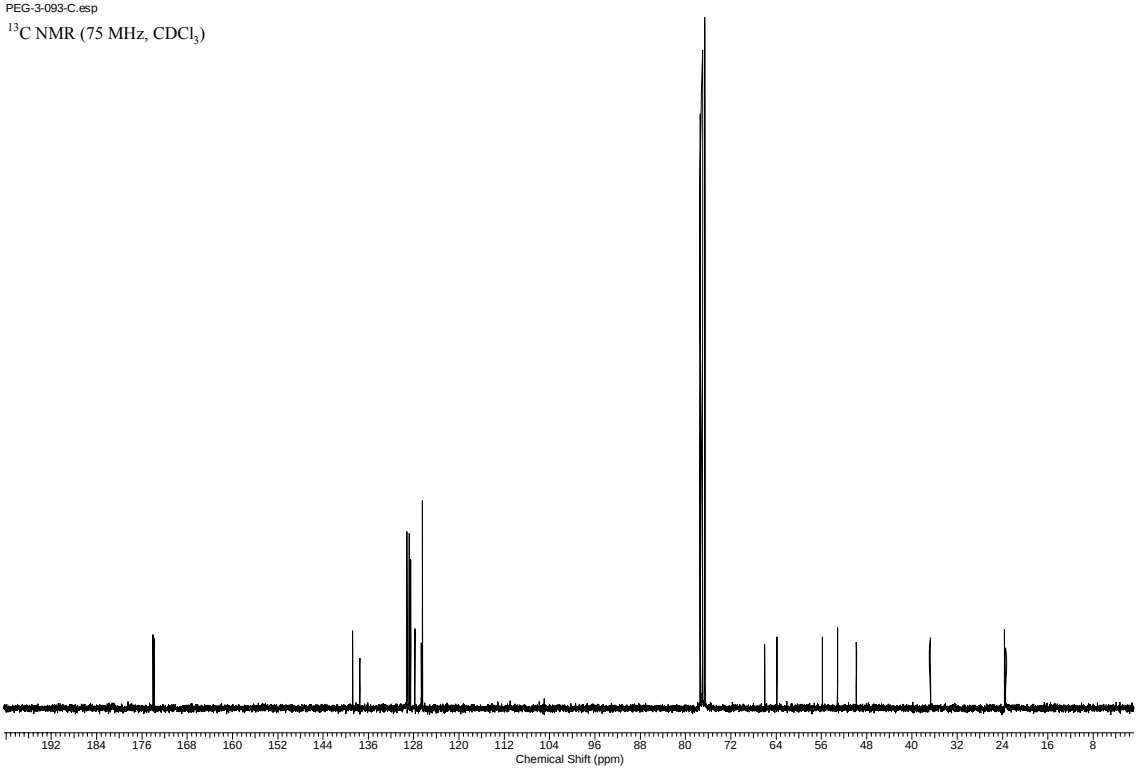


186



PEG-3-093-C.esp

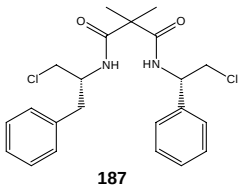
^{13}C NMR (75 MHz, $CDCl_3$)



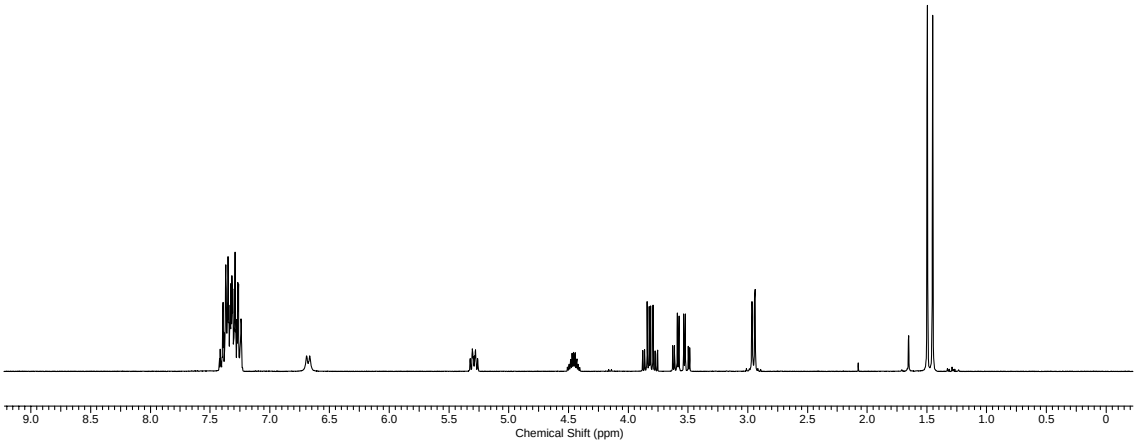
N^1-((S)-2-Chloro-1-phenylethyl)-N^3-((R)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethyl malonamide 187

3110H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

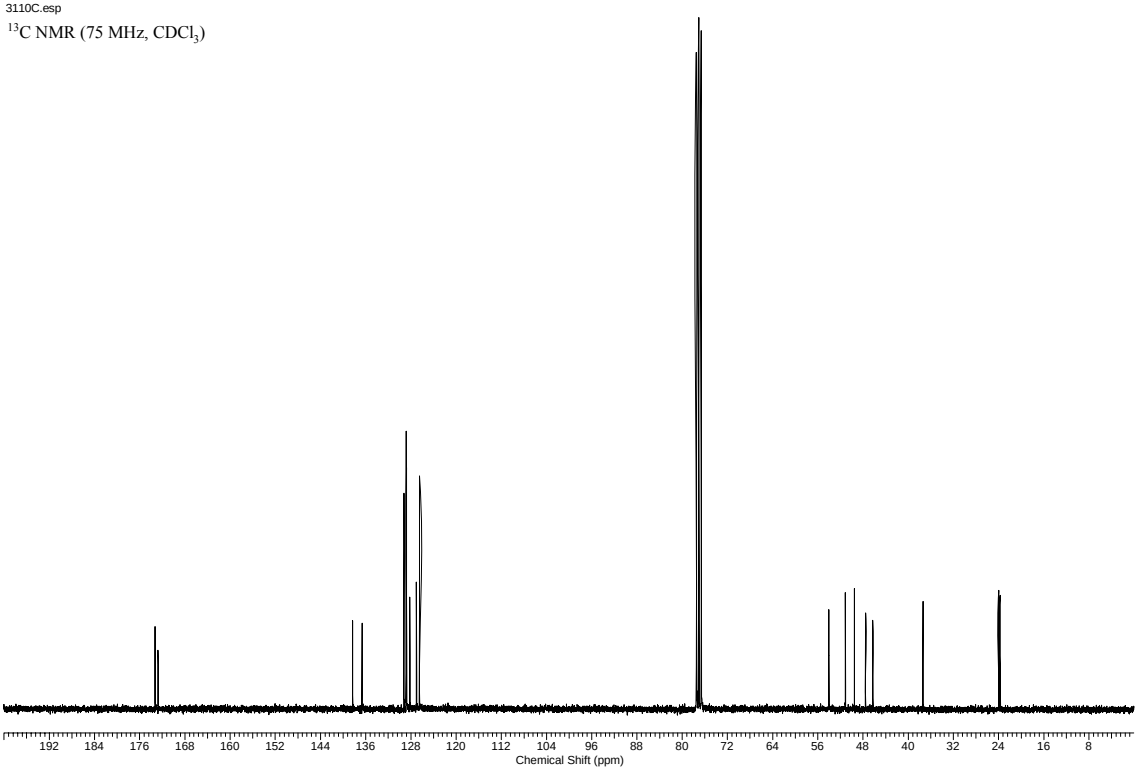


187



3110C.esp

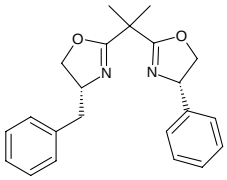
^{13}C NMR (75 MHz, $CDCl_3$)



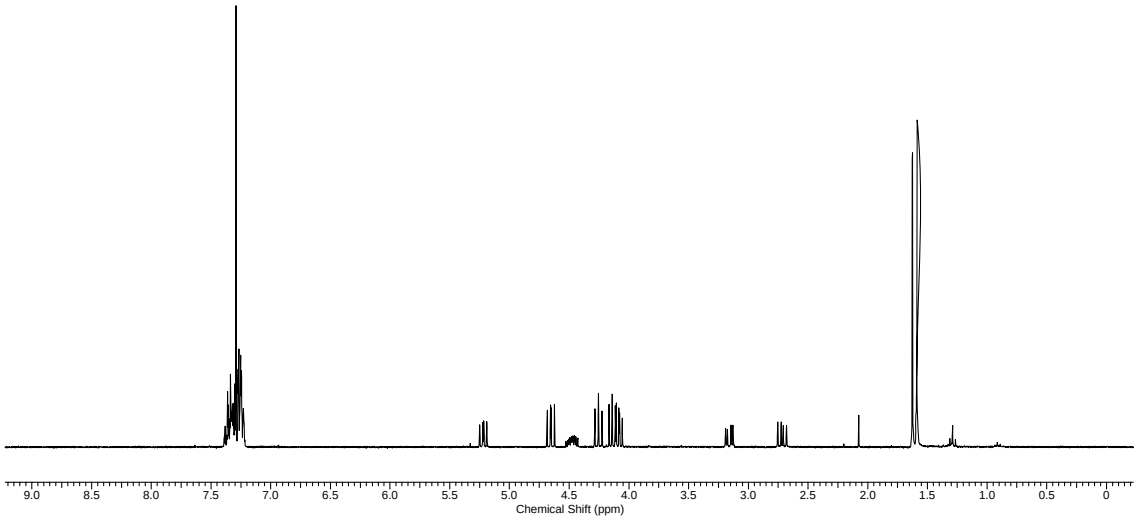
(R)-4-Benzyl-2-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole 181

3112H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

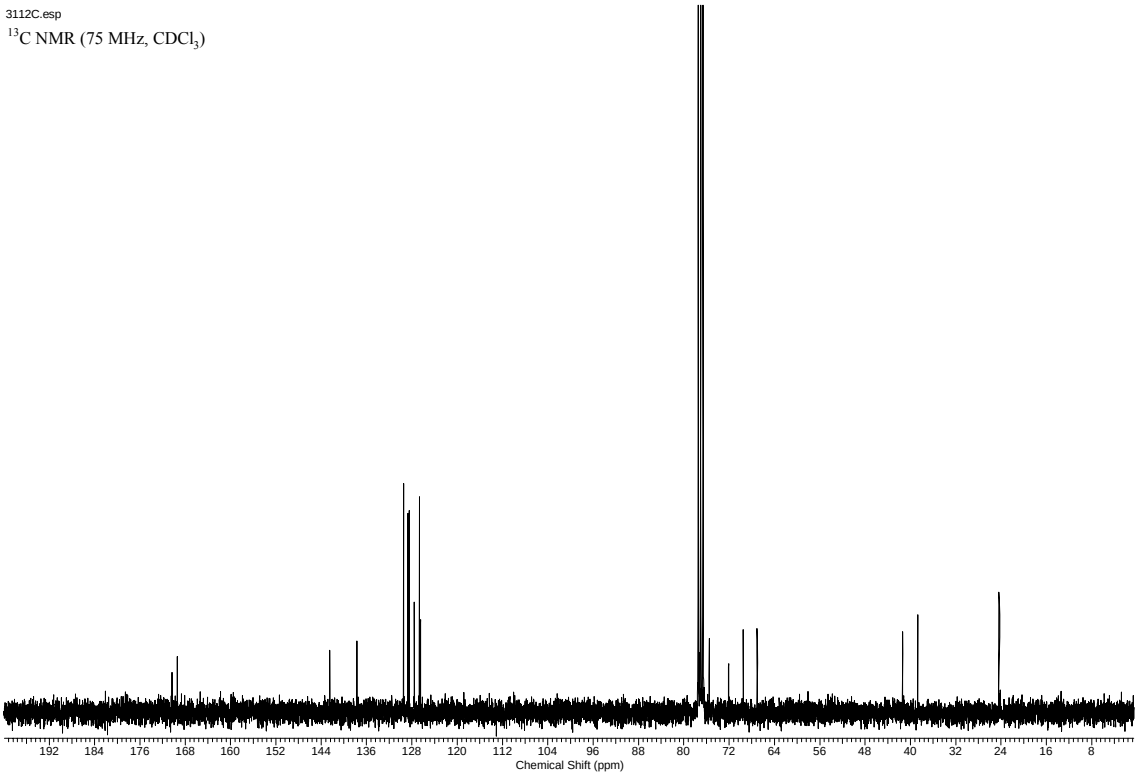


181



3112C.esp

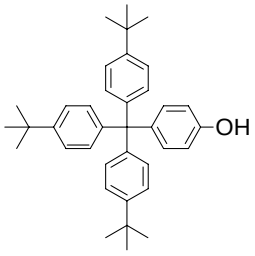
^{13}C NMR (75 MHz, $CDCl_3$)



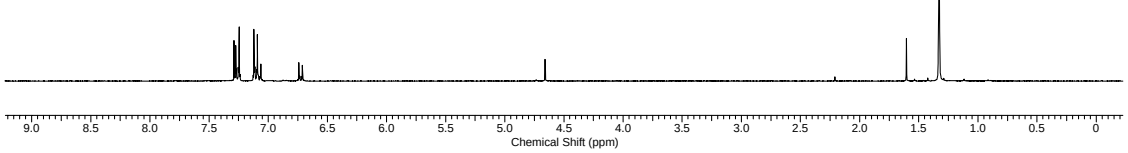
*4-(Tris(4-*tert*-butylphenyl)methyl)phenol 196*

PEG-3-071-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

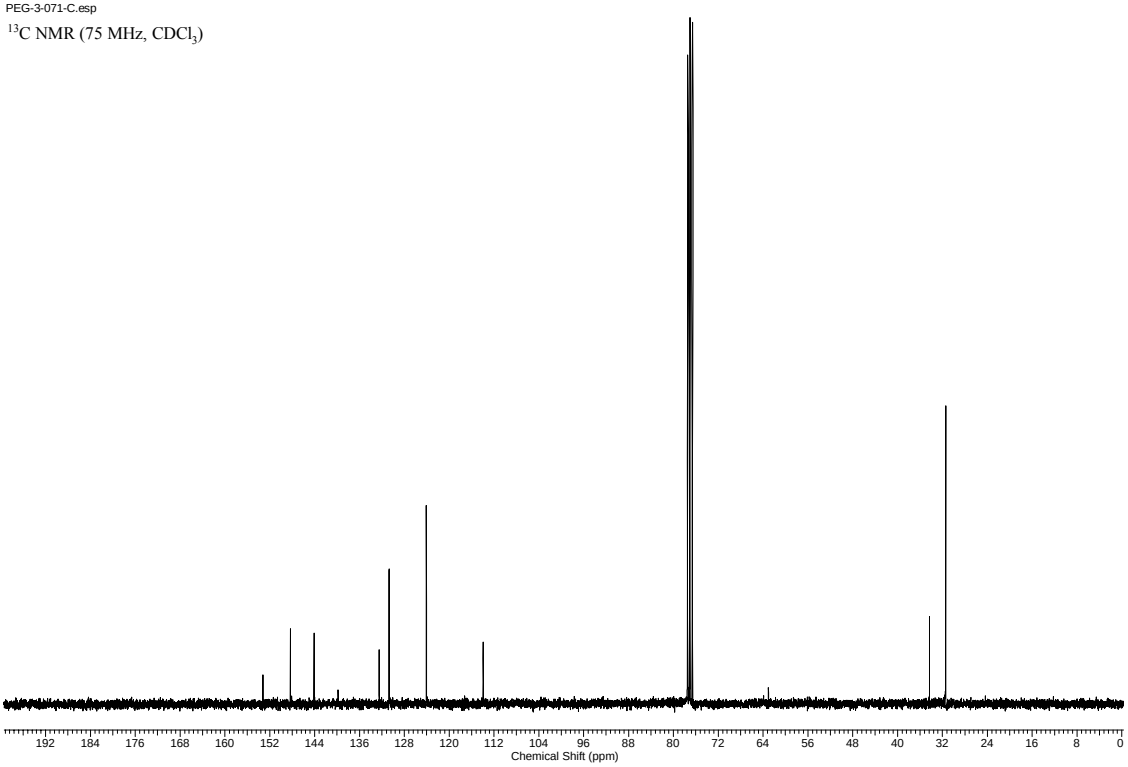


196



PEG-3-071-C.esp

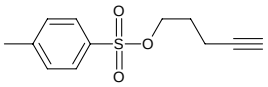
^{13}C NMR (75 MHz, $CDCl_3$)



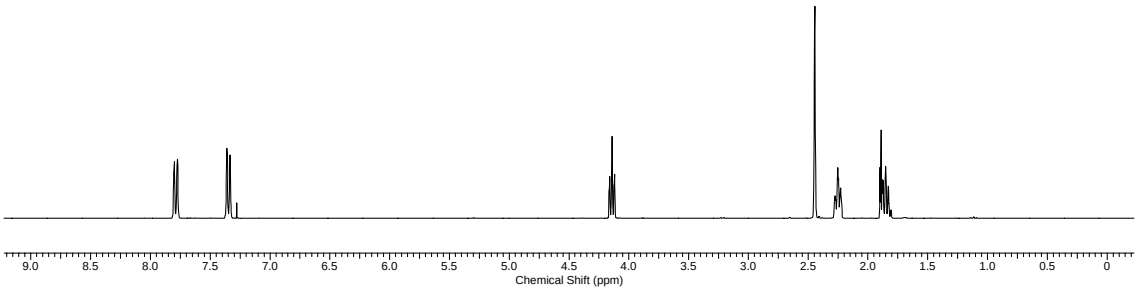
Pent-4-ynyl 4-methylbenzenesulfonate 197

peg-1-147a-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

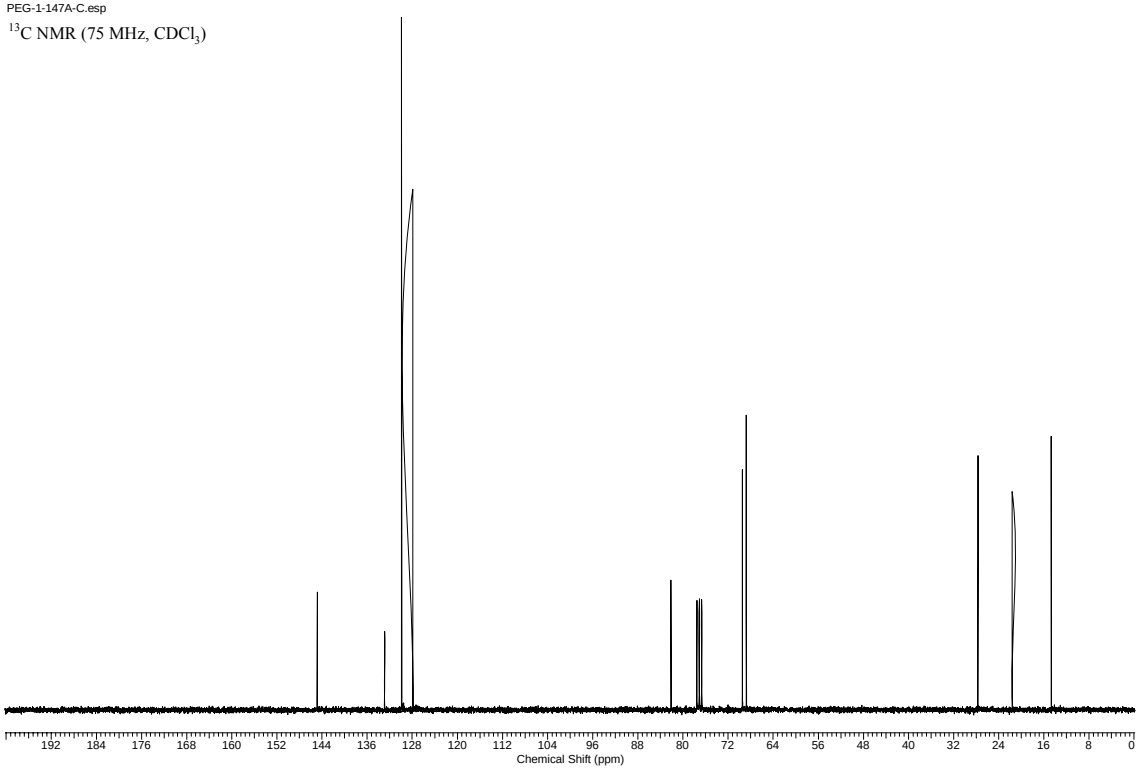


197



PEG-1-147A-C.esp

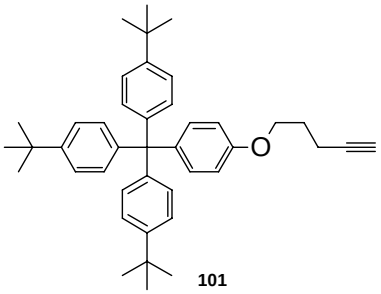
^{13}C NMR (75 MHz, $CDCl_3$)



*4,4',4''-((4-(Pent-4-ynyloxy)phenyl)methanetriyl)tris(*tert-*butylbenzene) 101*

pegh3155a H.esp

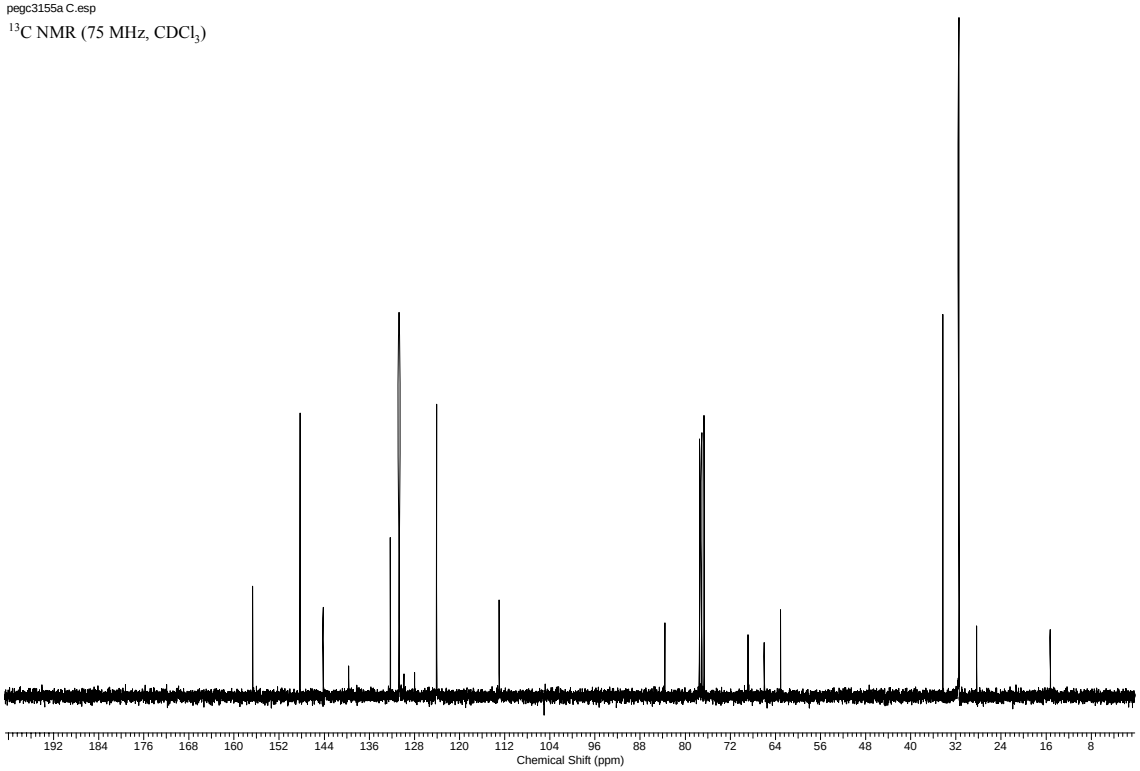
^{1}H NMR (300 MHz, $CDCl_3$)



101

pegc3155a C.esp

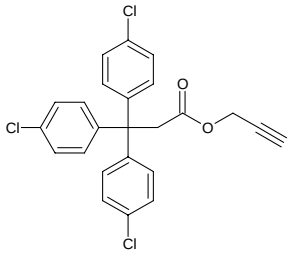
^{13}C NMR (75 MHz, $CDCl_3$)



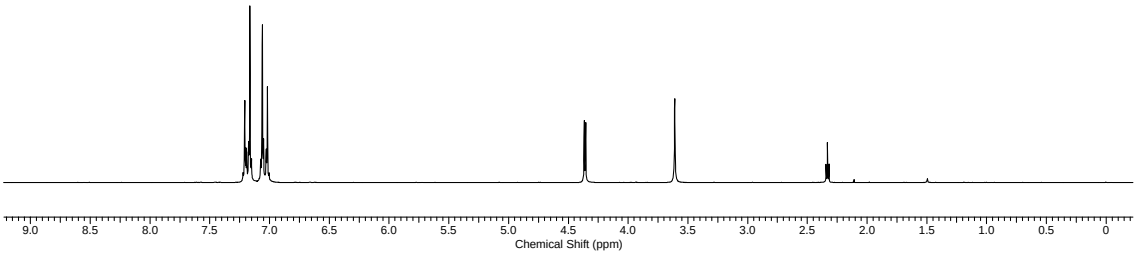
Prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate 200

PEG-1-006-H.esp

^{1}H NMR (400 MHz, C_3D_6O)

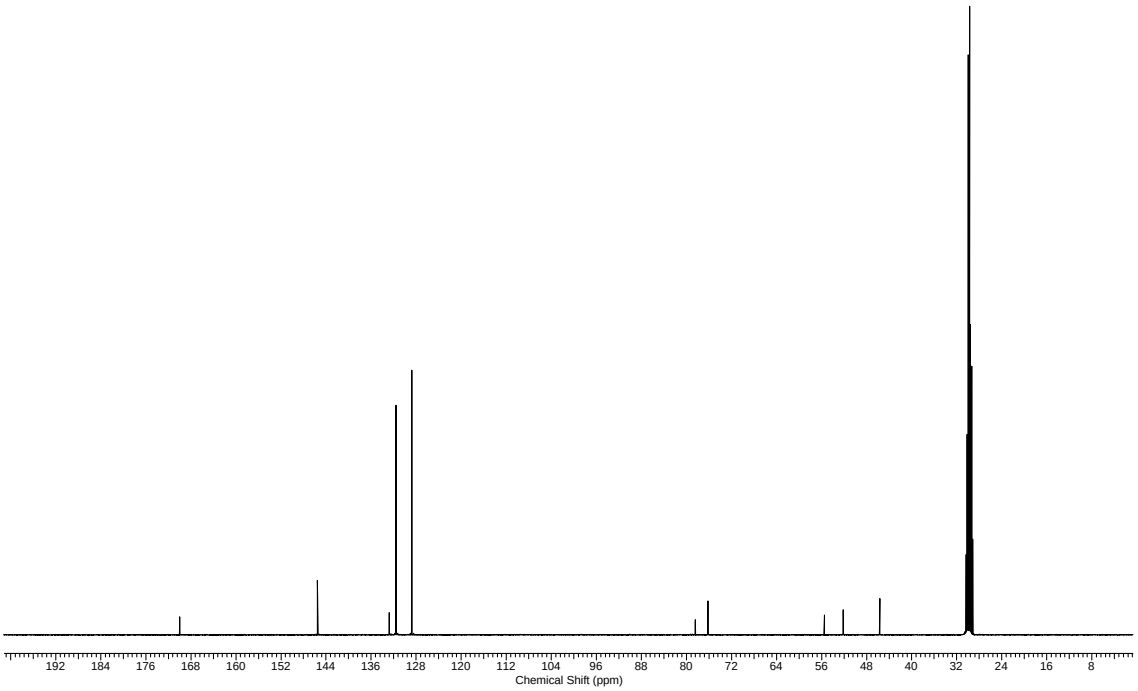


200



pegc1006b.001.esp

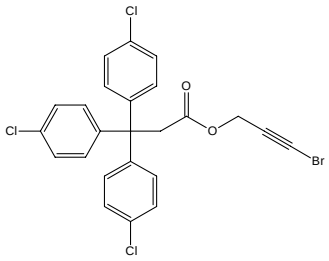
^{13}C NMR (101 MHz, C_3D_6O)



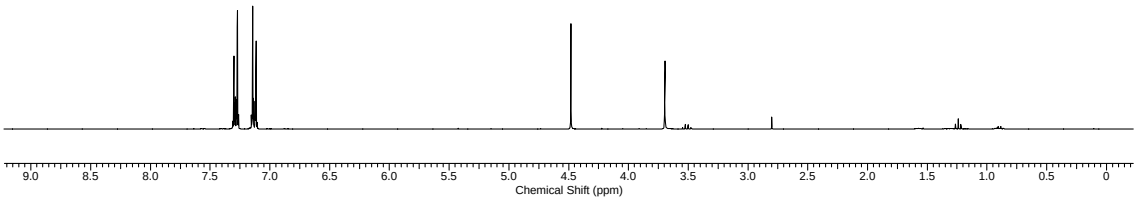
3-Bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate 201

3014.esp

^{1}H NMR (300 MHz, $CDCl_3$)

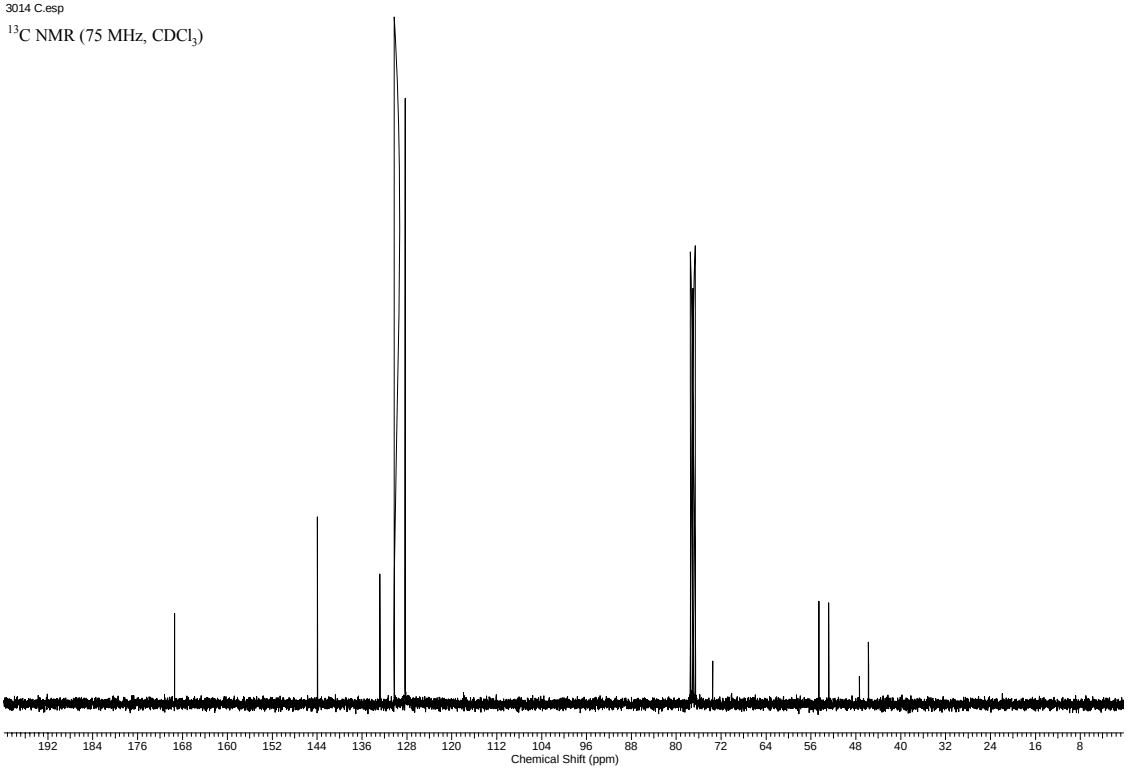


201



3014 C.esp

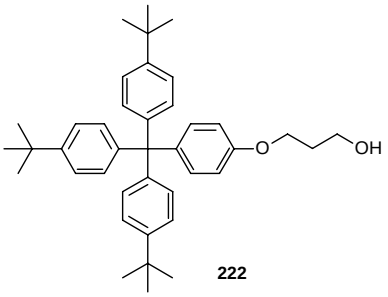
^{13}C NMR (75 MHz, $CDCl_3$)



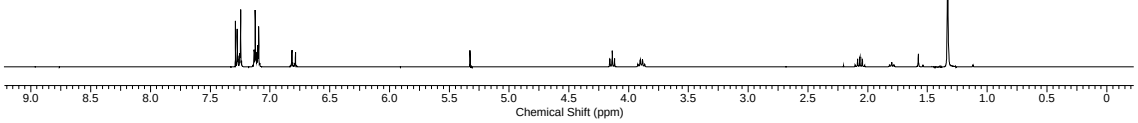
*3-(4-(Tris(4-*tert*-butylphenyl)methyl)phenoxy)propan-1-ol 222*

3141H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

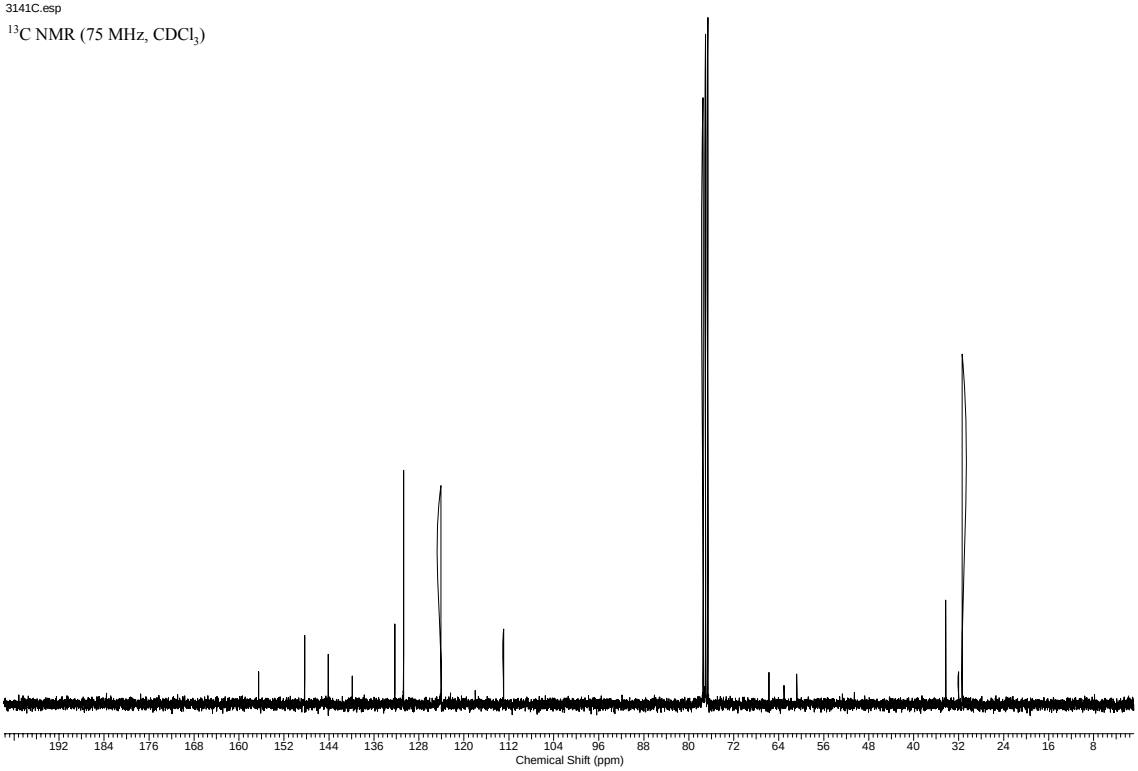


222



3141C.esp

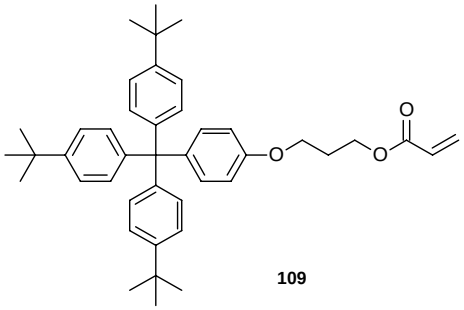
^{13}C NMR (75 MHz, $CDCl_3$)



*3-(4-(Tris(4-*tert*-butylphenyl)methyl)phenoxy)propyl acrylate 109*

PEG-3-031-H.esp

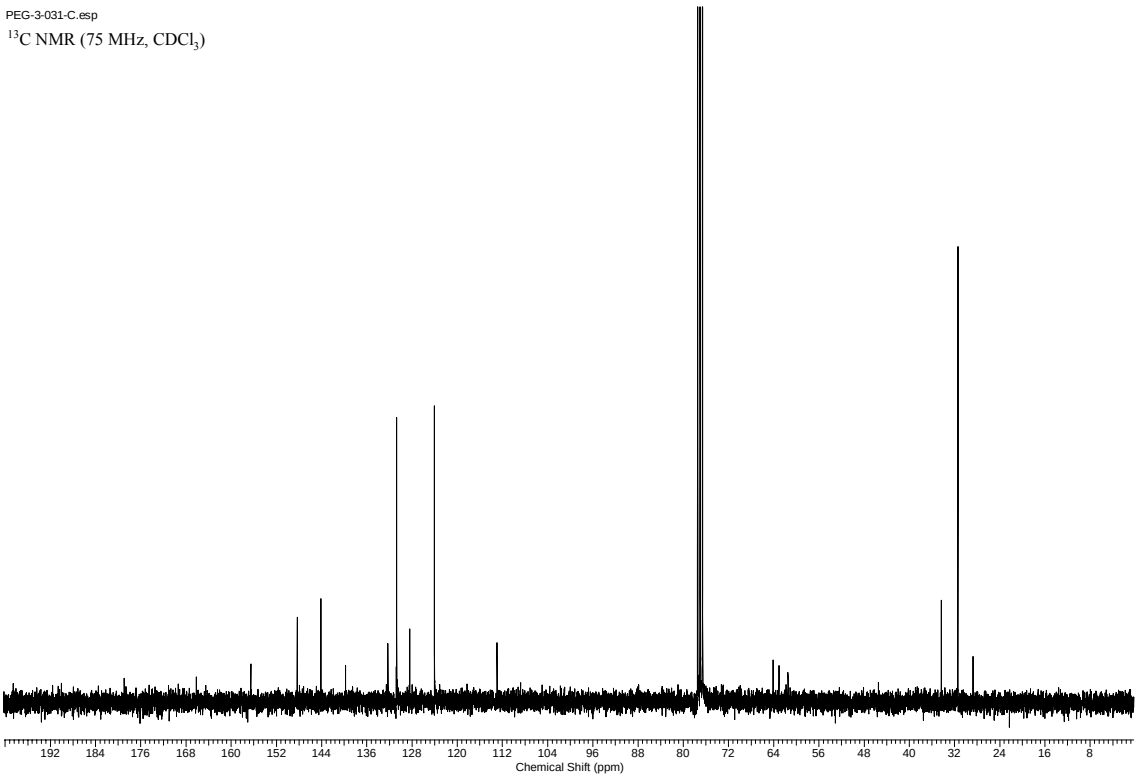
^{1}H NMR (300 MHz, $CDCl_3$)



109

PEG-3-031-C.esp

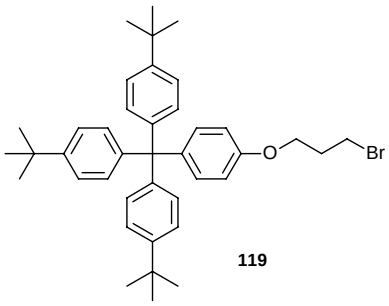
^{13}C NMR (75 MHz, $CDCl_3$)



*4,4',4''-((4-(3-Bromopropoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 119*

PEG-3-072-H.esp

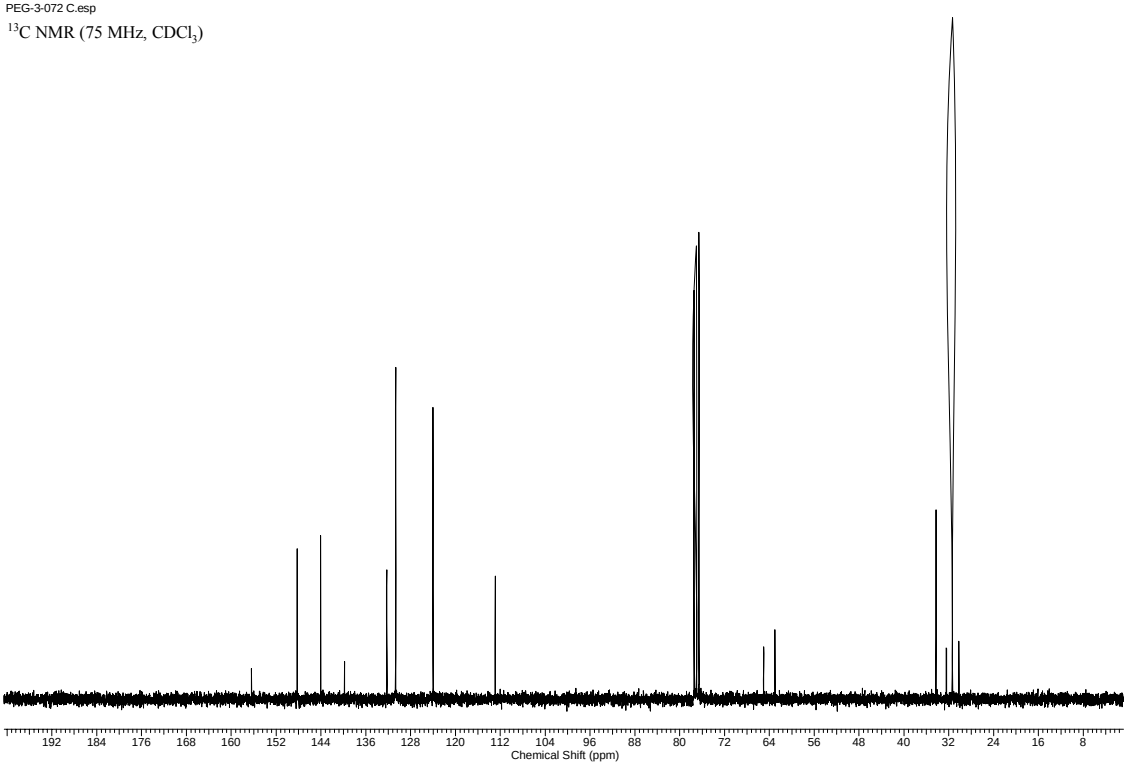
^{1}H NMR (300 MHz, $CDCl_3$)



119

PEG-3-072 C.esp

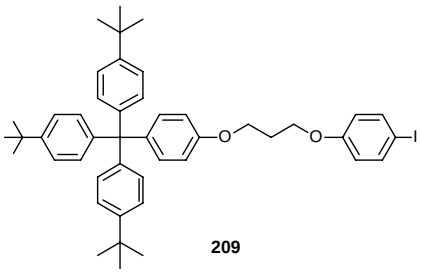
^{13}C NMR (75 MHz, $CDCl_3$)



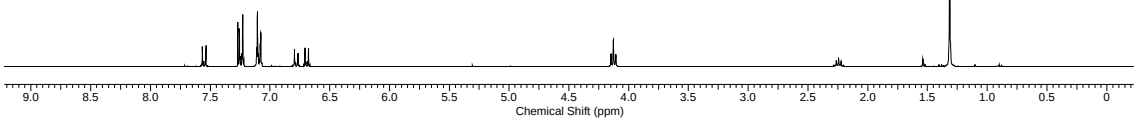
*4,4',4''-((4-(3-(4-Iodophenoxy)propoxy)phenyl)methanetriyl)tris(*tert*-butylbenzene) 209*

PEG-3-067-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

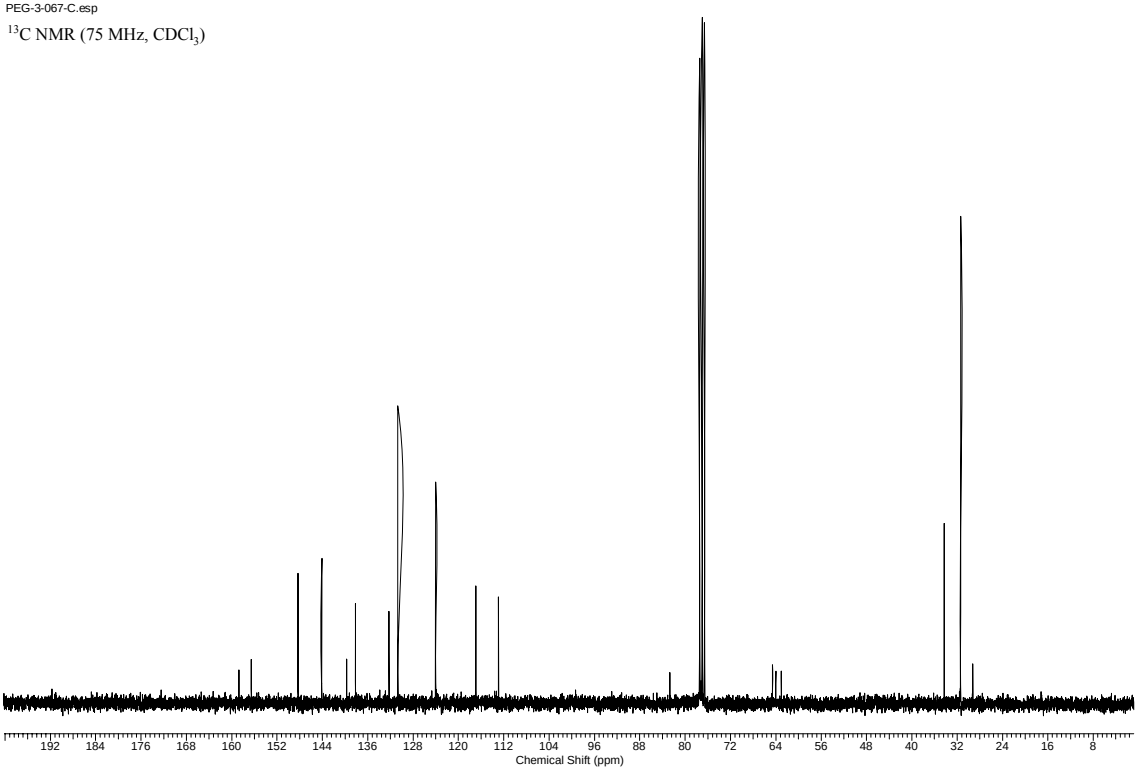


209



PEG-3-067-C.esp

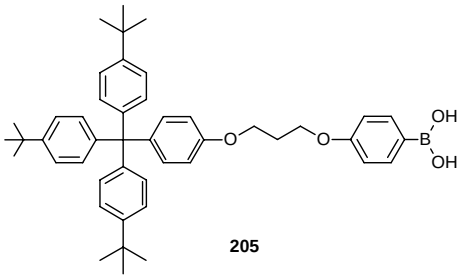
^{13}C NMR (75 MHz, $CDCl_3$)



*4-(3-(4-(Tris(4-*tert*-butylphenyl)methyl)phenoxy)propoxy)phenylboronic acid 205*

3-032-H.esp

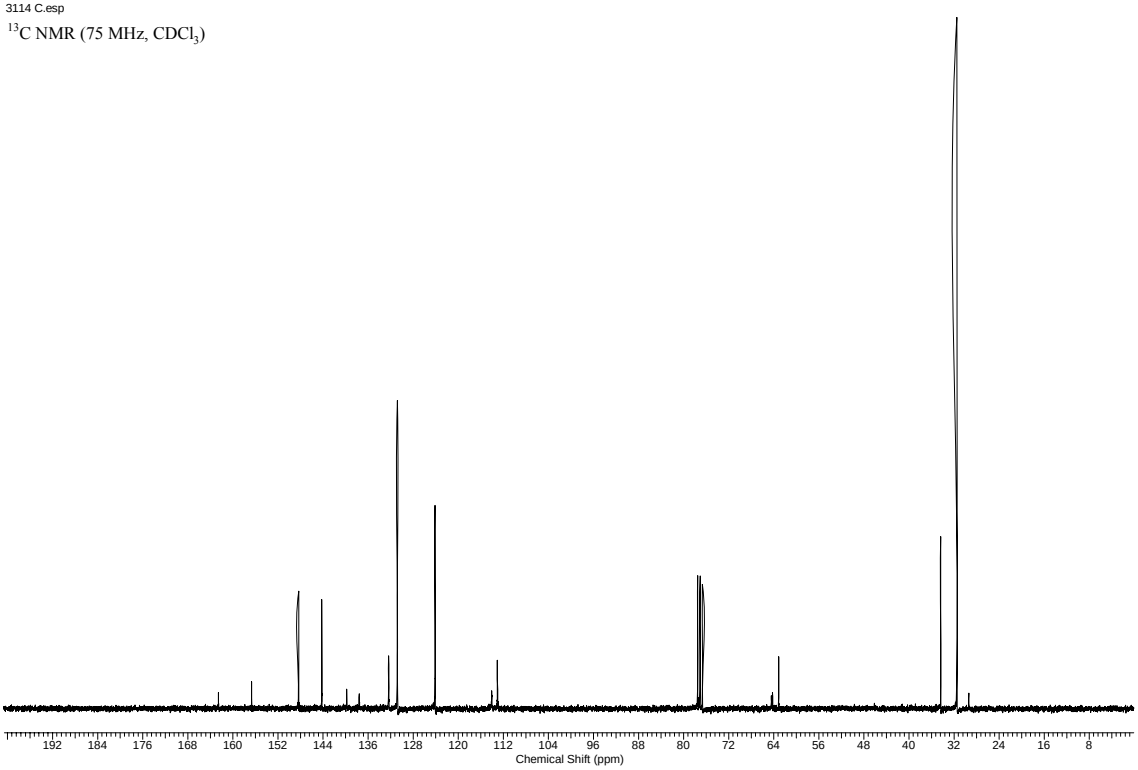
^{1}H NMR (300 MHz, $CDCl_3$)



205

3114 C.esp

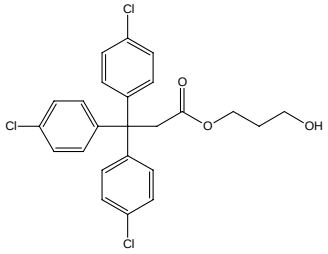
^{13}C NMR (75 MHz, $CDCl_3$)



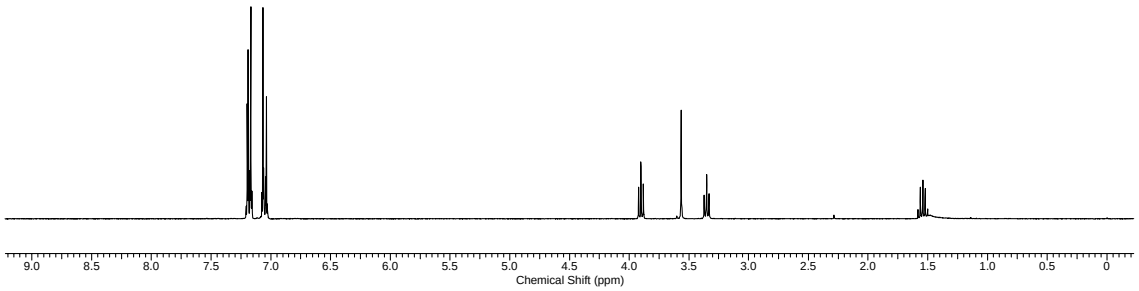
3-Hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate 211

PEG-3-036-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

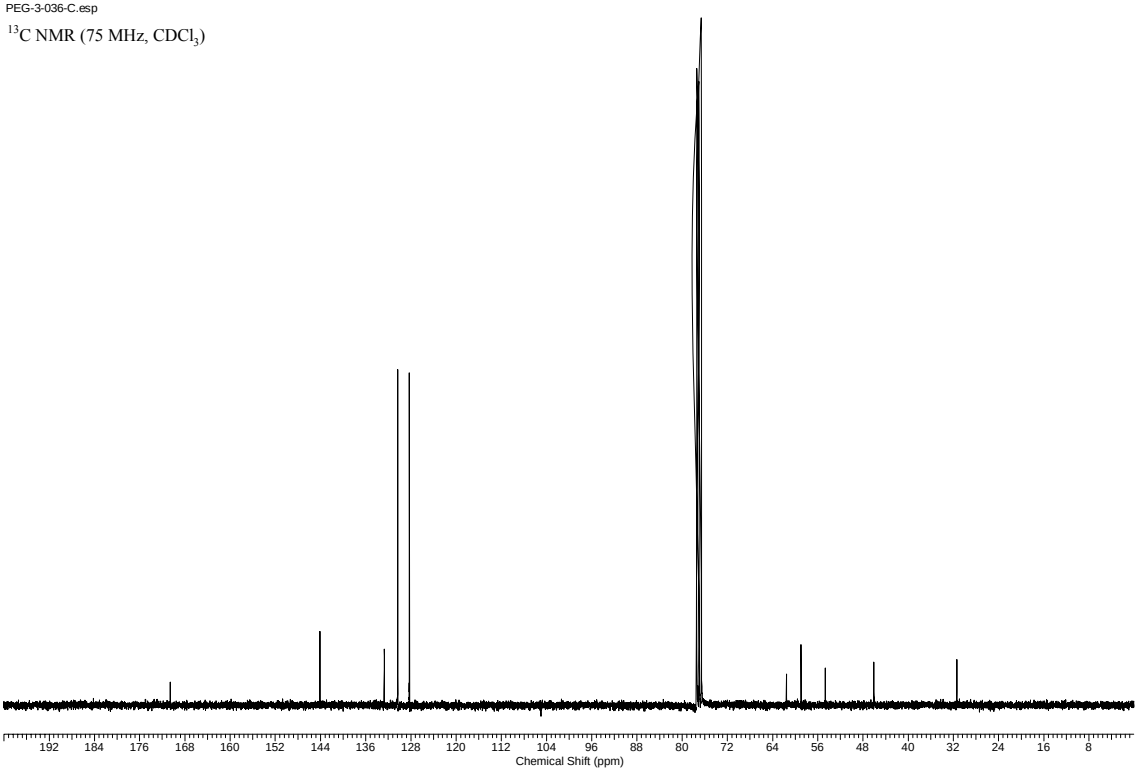


211



PEG-3-036-C.esp

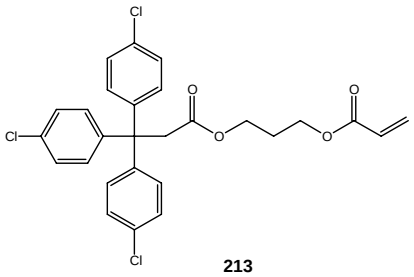
^{13}C NMR (75 MHz, $CDCl_3$)



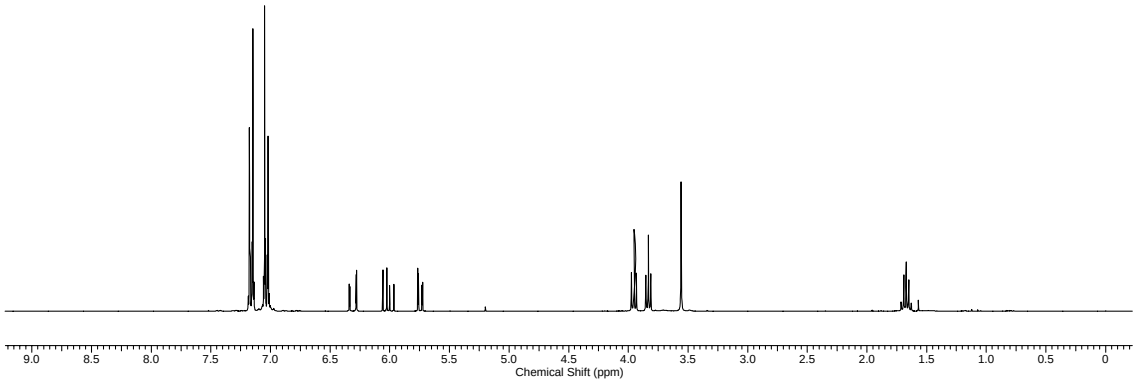
3-(3,3,3-Tris(4-chlorophenyl)propanoyloxy)propyl acrylate 213

PEG-3-066-H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

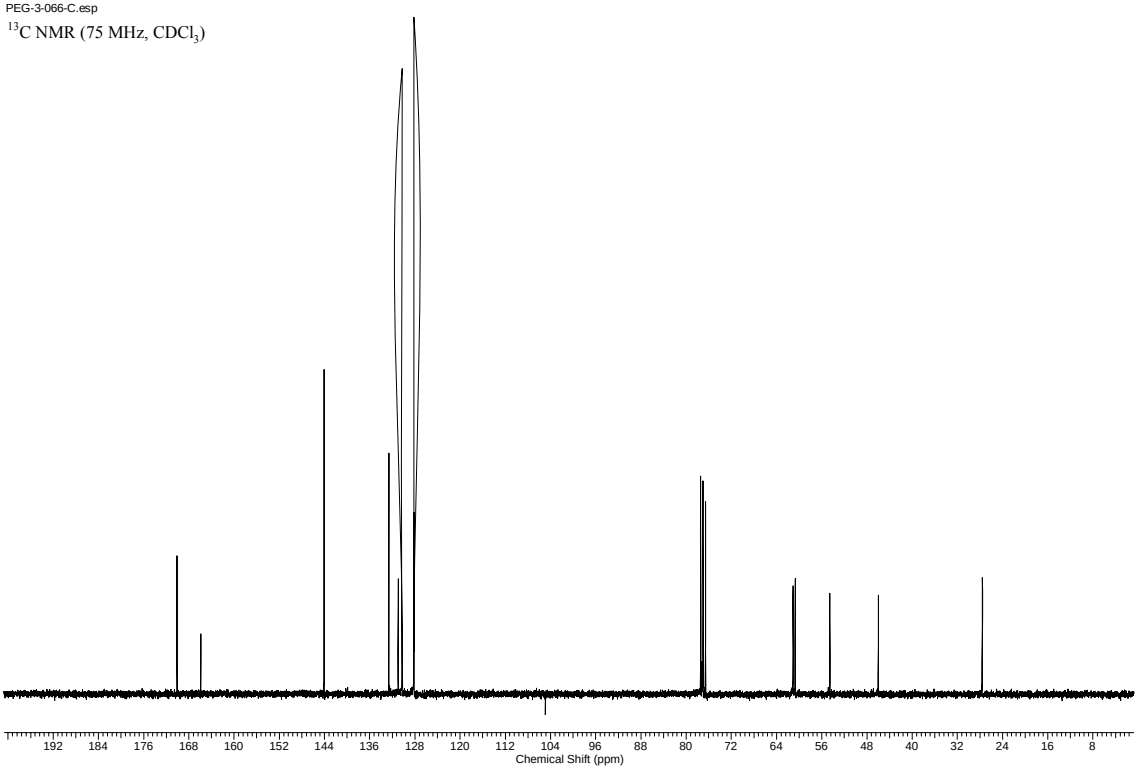


213



PEG-3-066-C.esp

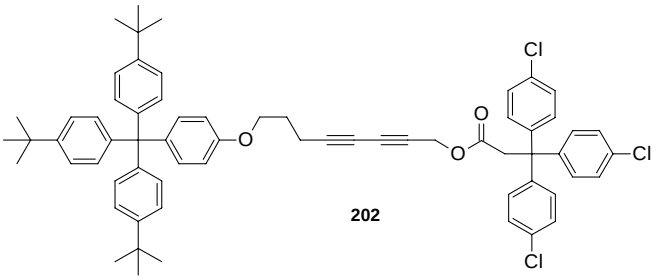
^{13}C NMR (75 MHz, $CDCl_3$)



Thread 202

3015d.esp

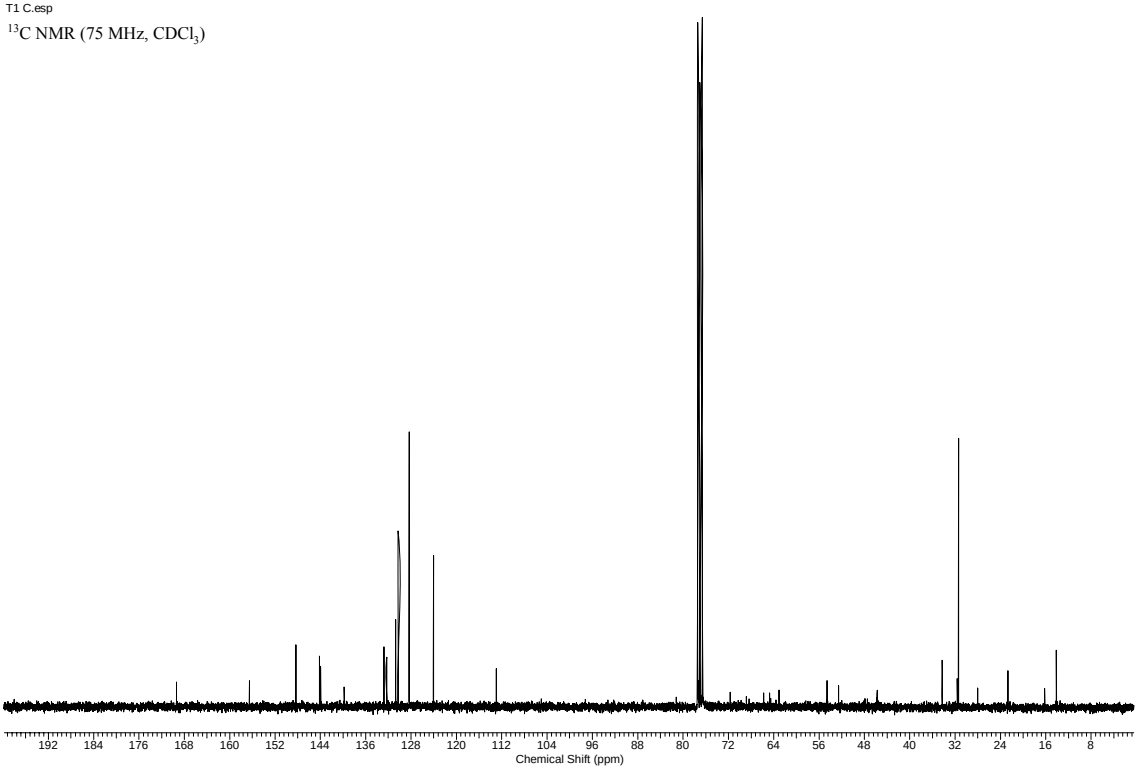
^{1}H NMR (300 MHz, $CDCl_3$)



202

T1 C.esp

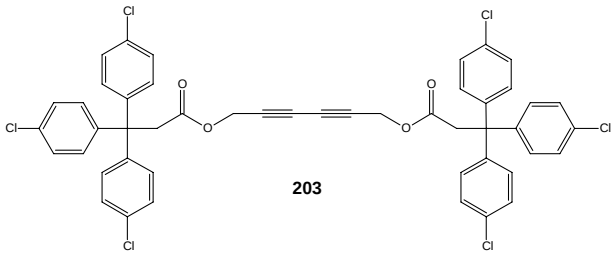
^{13}C NMR (75 MHz, $CDCl_3$)



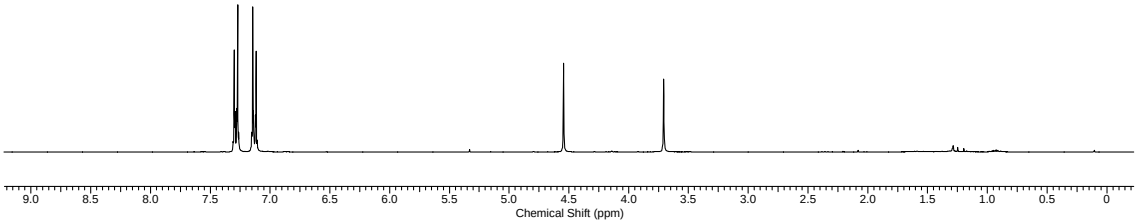
Thread 203

T3 H.esp

^{1}H NMR (300 MHz, $CDCl_3$)

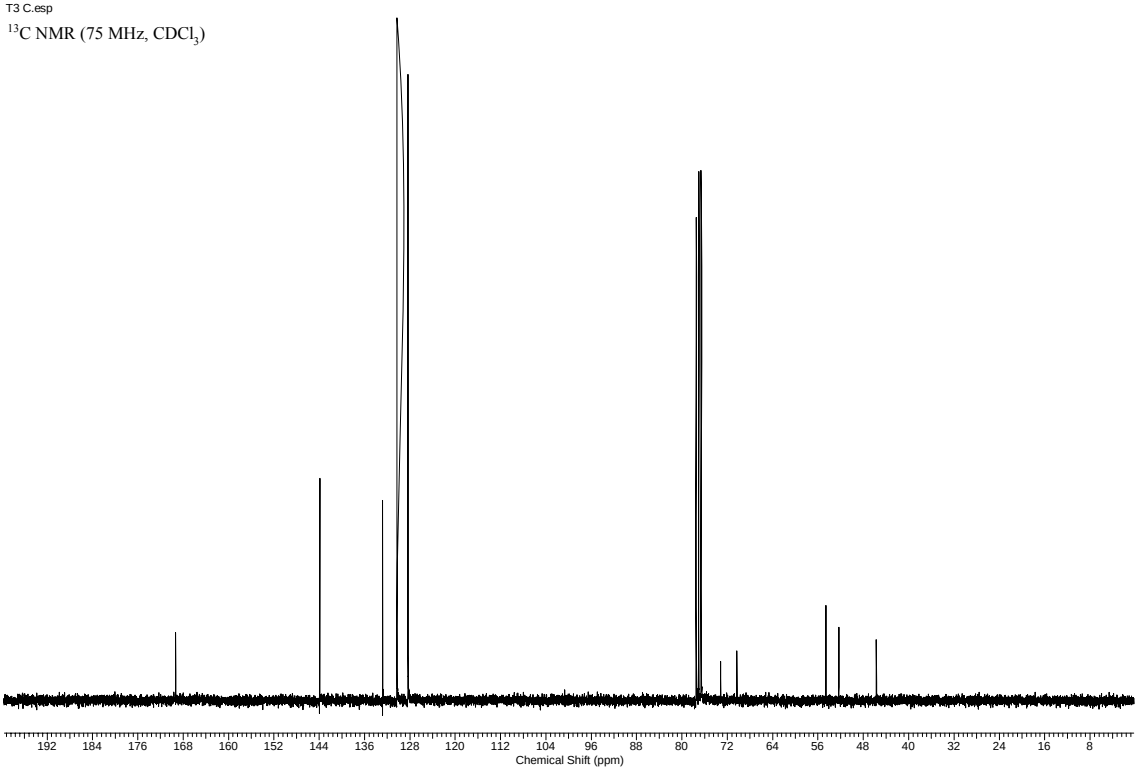


203



T3 C.esp

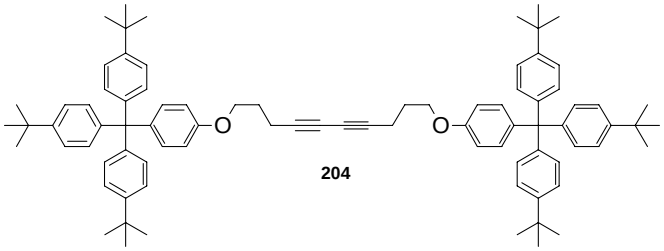
^{13}C NMR (75 MHz, $CDCl_3$)



Thread 204

T2 H.esp

^{1}H NMR (300 MHz, $CDCl_3$)



204

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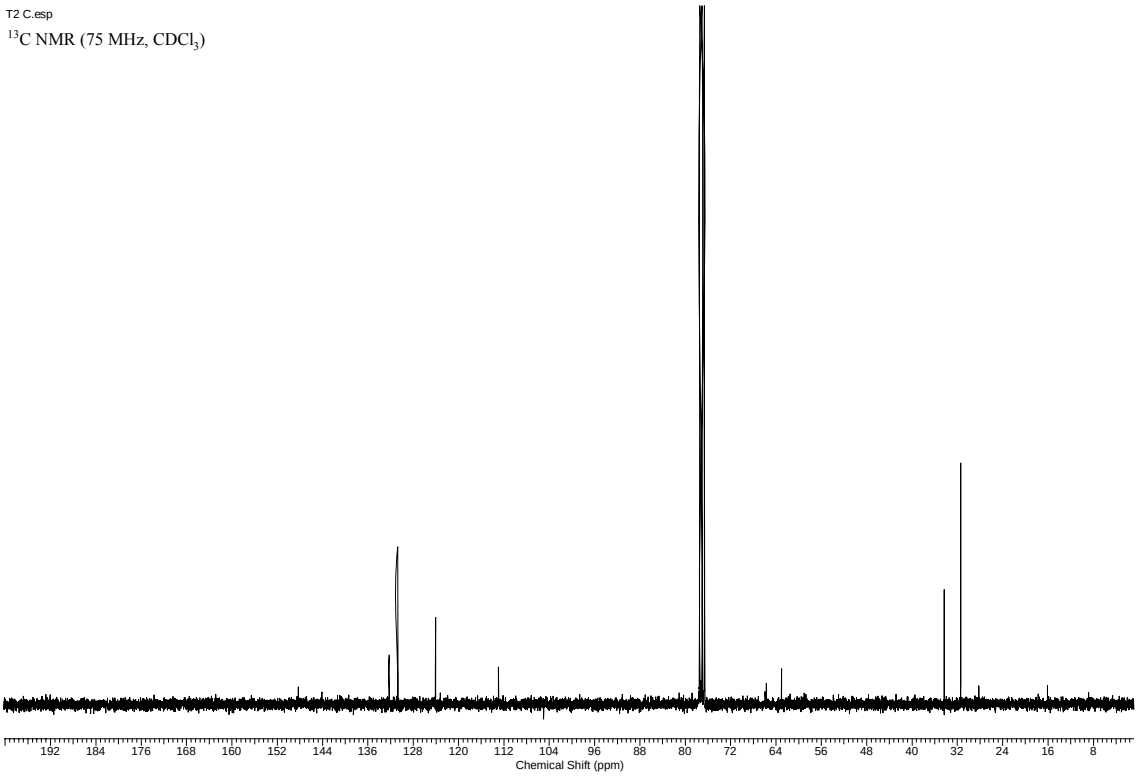
^{13}C NMR (75 MHz, $CDCl_3$)



Thread 214

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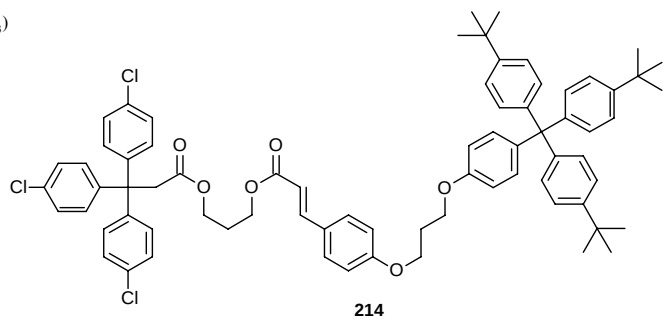

214

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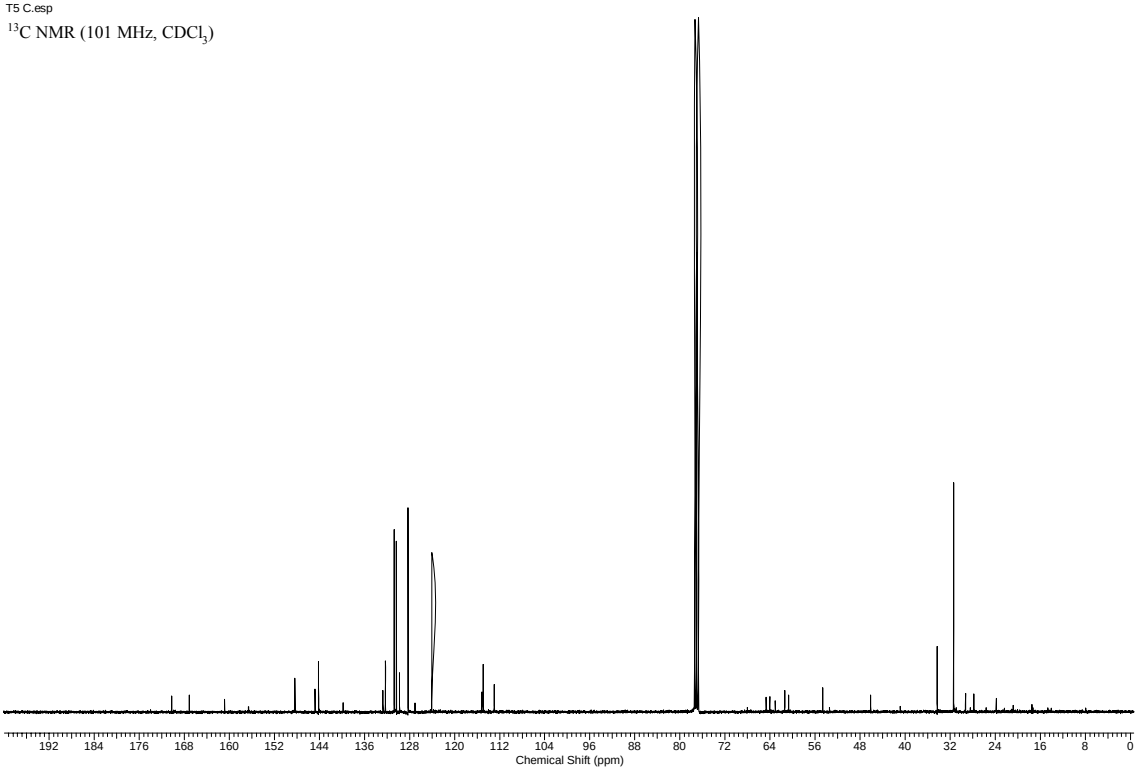
^{13}C NMR (101 MHz, $CDCl_3$)



Thread 219

T7 H.esp

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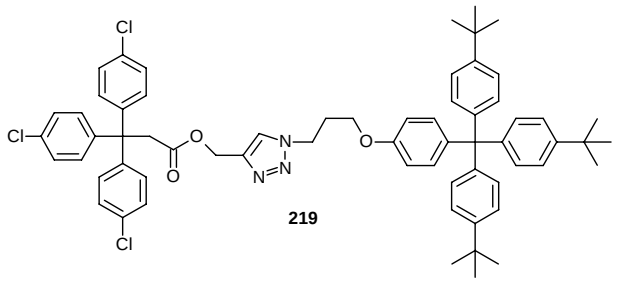

219

T7 C.esp

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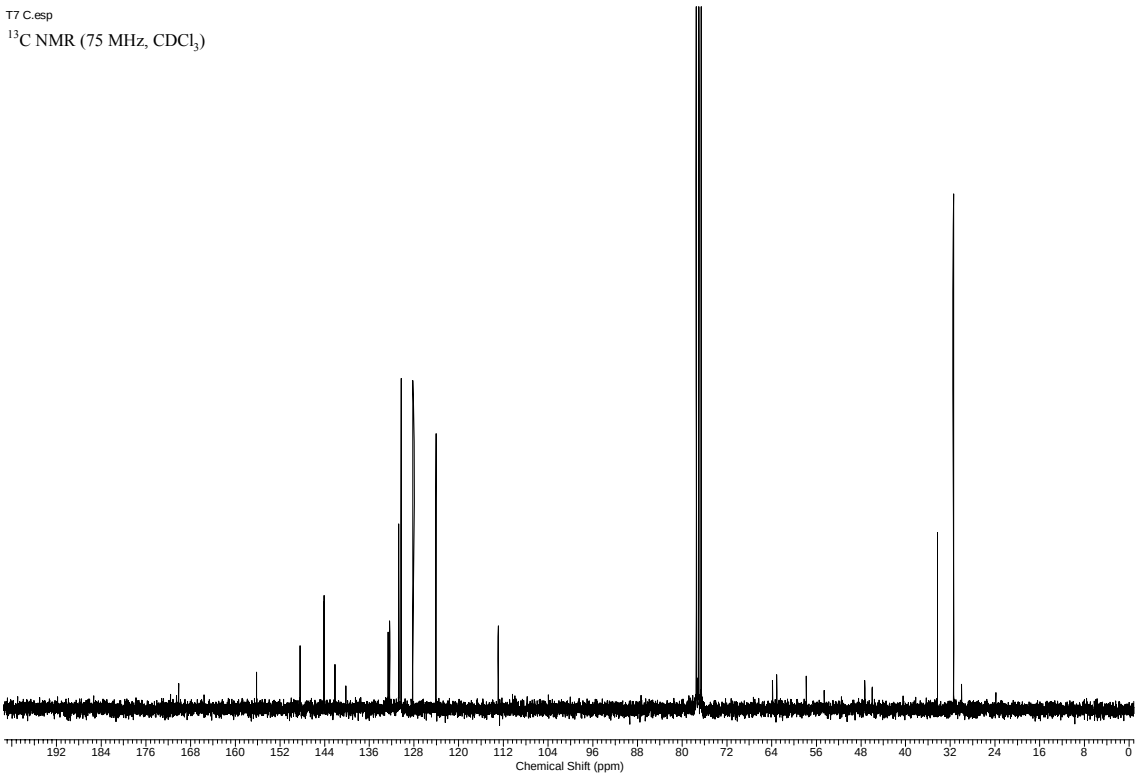
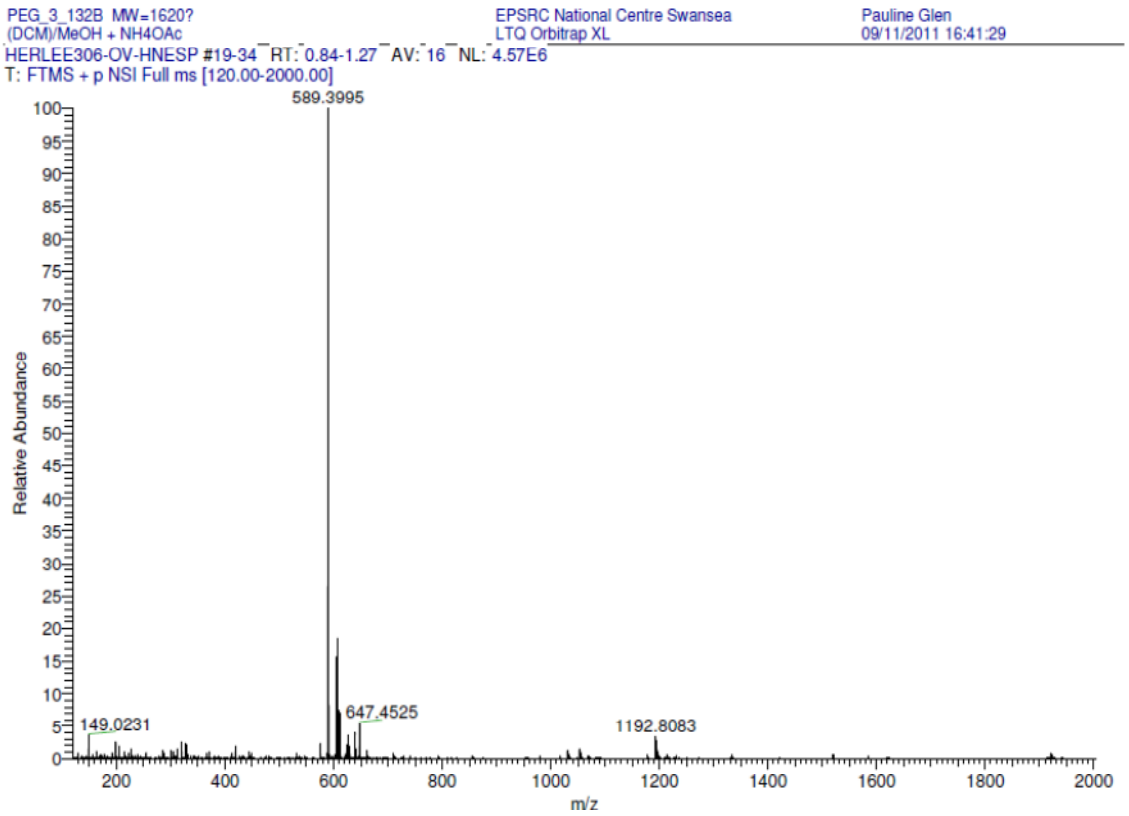


Appendix B: Mass Spectrum of Rotaxane 215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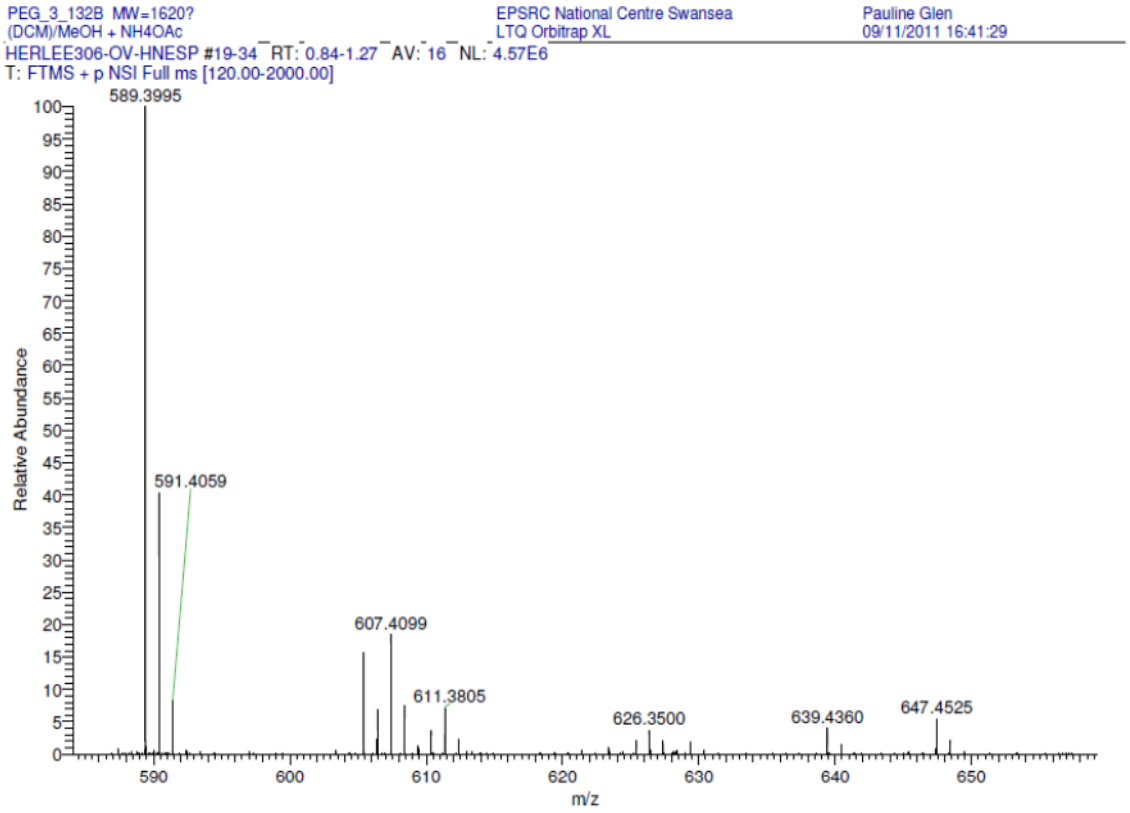
(DCM)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Pauline Glen
09/11/2011 16:41:29
HERLEE306-OV-HNESP #19-34 RT: 0.84-1.27 AV: 16 NL: 4.57E6
T: FTMS + p NSI Full ms [120.00-2000.00]
589.3995
647.4525
149.0231
1192.8083
Relative Abundance
m/z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LTQ Orbitrap XL
Pauline Glen
09/11/2011 16:41:29
HERLEE306-OV-HNESP #19-34 RT: 0.84-1.27 AV: 16 NL: 4.57E6
T: FTMS + p NSI Full ms [120.00-2000.00]
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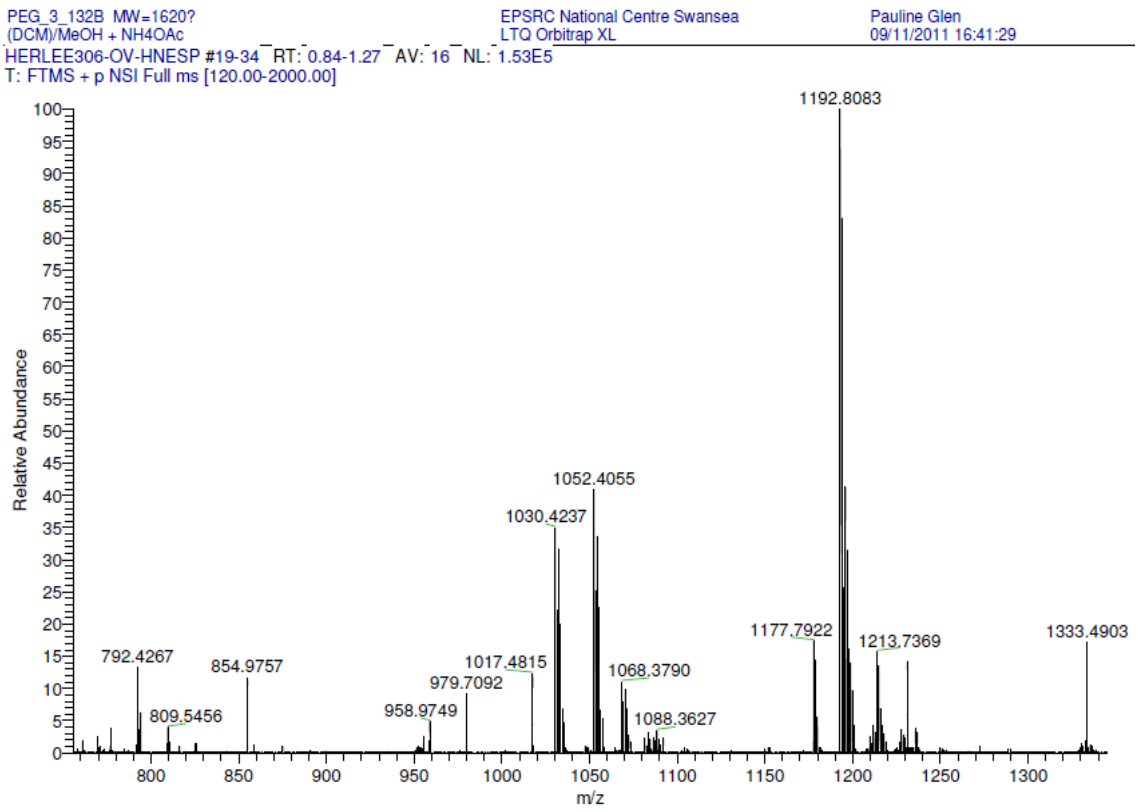
591.4059
607.4099
611.3805
626.3500
639.4360
647.4525
Relative Abundance
m/z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(DCM)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Pauline Glen
09/11/2011 16:41:29
HERLEE306-OV-HNESP #19-34 RT: 0.84-1.27 AV: 16 NL: 1.53E5
T: FTMS + p NSI Full ms [120.00-2000.00]
Relative Abundance
m/z
1192.8083
1052.4055
1030.4237
1177.7922
1213.7369
1333.4903
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854.9757
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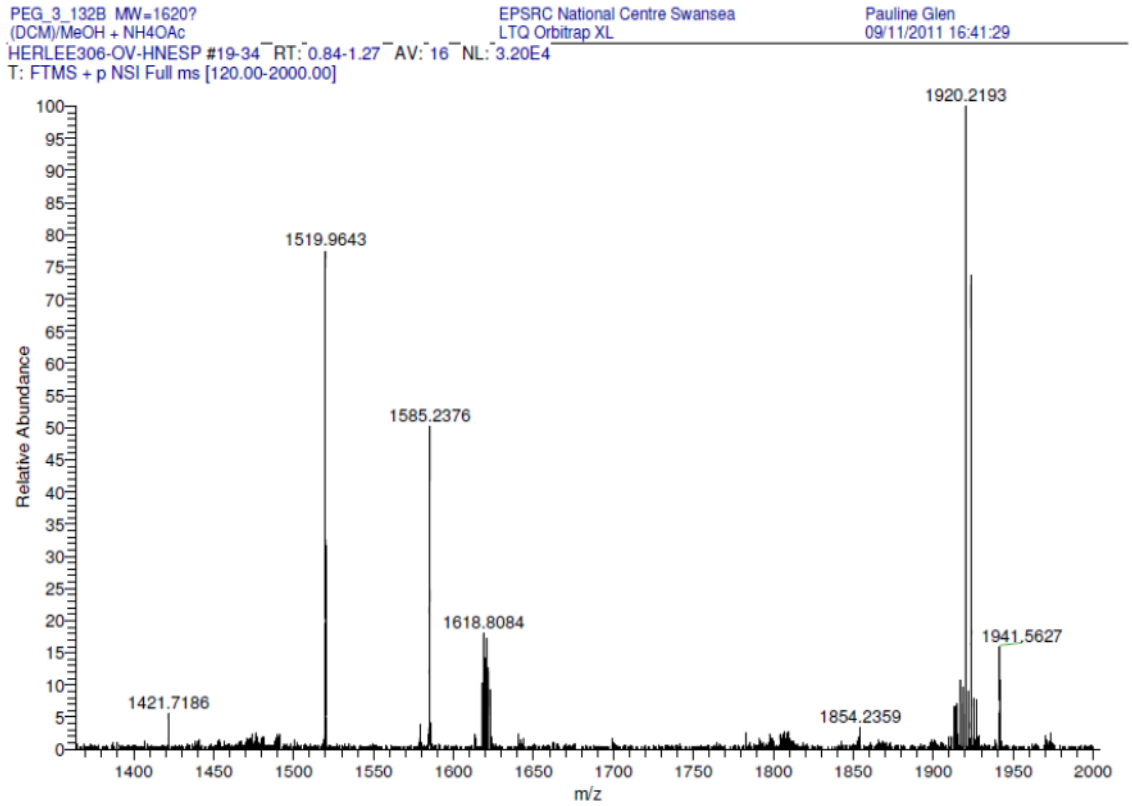
1068.3790
809.5456
958.9749
1088.3627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(DCM)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Pauline Glen
09/11/2011 16:41:29
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Relative Abundance
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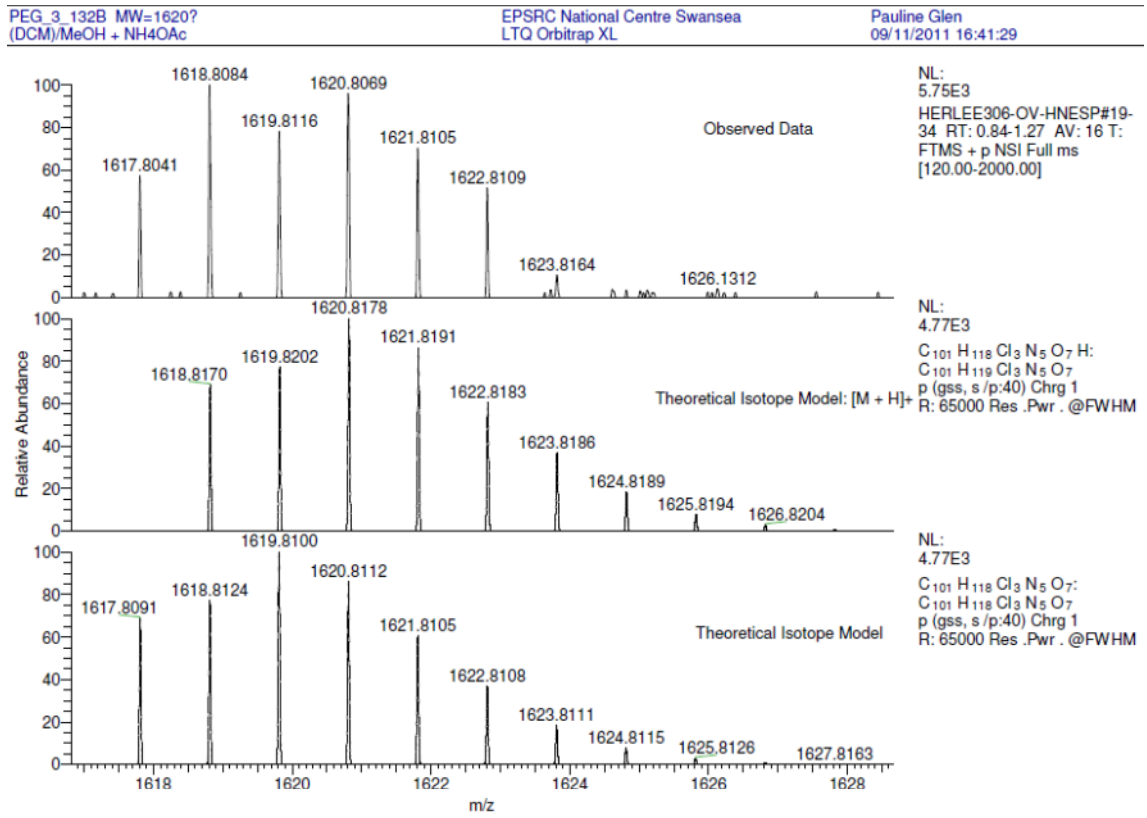
1519.9643
1585.2376
1618.8084
1941.5627
1421.7186
1854.2359


PEG_3_132B MW=1620?
(DCM)/MeOH + NH4OAc
EPSRC National Centre Swansea
LTQ Orbitrap XL
Pauline Glen
09/11/2011 16:41:29
Observed Data
NL:
5.75E3
HERLEE306-OV-HNESP#19-34 RT: 0.84-1.27 AV: 16 T: FTMS + p NSI Full ms [120.00-2000.00]
1618.8084
1620.8069
1619.8116
1621.8105
1617.8041
1622.8109
1623.8164
1626.1312
Theoretical Isotope Model: [M + H]+
NL:
4.77E3
C101 H118 Cl3 N5 O7 H:
C101 H119 Cl3 N5 O7
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R: 65000 Res .Pwr . @FWHM
1620.8178
1621.8191
1619.8202
1618.8170
1622.8183
1623.8186
1624.8189
1625.8194
1626.8204
Theoretical Isotope Model
NL:
4.77E3
C101 H118 Cl3 N5 O7:
C101 H118 Cl3 N5 O7
p (gss, s /p:40) Chrg 1
R: 65000 Res .Pwr . @FWHM
1619.8100
1620.8112
1618.8124
1617.8091
1621.8105
1622.8108
1623.8111
1624.8115
1625.8126
1627.8163
Relative Abundance
m/z
1618
1620
1622
1624
1626
1628

Appendix C: Published Paper

Tetrahedron 69 (2013) 57–68

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of a C_1-symmetric Box macrocycle and studies towards active-template synthesis of mechanically planar chiral rotaxanes

Pauline E. Glen, James A.T. O'Neill, Ai-Lan Lee *

Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom

ARTICLE INFO

Article history:
Received 1 August 2012
Received in revised form 3 October 2012
Accepted 22 October 2012
Available online 30 October 2012

Keywords:
Macrocycles
Bis-oxazolines
Oxidative Heck
CuAAC click
Cadiot–Chodkiewicz
Rotaxane

ABSTRACT

A C_1-symmetric Box macrocycle has been synthesized for the first time. The Box macrocycle along with other C_1 and C_2-symmetric Box ligands were evaluated and compared as ligands in the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions as part of our studies towards achieving active-metal template synthesis of mechanically planar chiral rotaxanes. This study constitutes the first report of Cadiot–Chodkiewicz and CuAAC 'click' reactions using Box ligands, as well as the first dedicated study of oxidative Heck reactions using Box ligands.

1. Introduction

The synthesis of interlocked molecules such as catenanes and rotaxanes is of great contemporary interest to chemists due not only to their peculiar structures but also their potential applications in nanotechnology—for example, as molecular machines, switches, wires and motors.[1] Additionally, rotaxanes and knots found in nature exhibit remarkable activities compared with linear analogues.[2] So far, however, much less attention has been paid to one of the most interesting and yet least exploited features of interlocked architectures: their chirality—a rotaxane can possess *mechanical planar chirality* (sometimes referred to as 'cyclochirality')[3] even if both the wheel and axle are achiral themselves.[3] This inherent chirality arises if there is dissymmetry in both the ring and the thread, for example, if both the axle and the wheel bear groups, which impart directionality (Fig. 1). Planar chiral rotaxanes have seen application as chiral sensors for amino acids,[4c] and other chiral rotaxanes have shown promise in asymmetric catalysis applications.[5] To date, however, only one attempt at an enantioselective synthesis of mechanically planar chiral rotaxanes has been reported, yielding an optically active rotaxane in only 4.4% ee.[6] Prior to that, optically active planar chiral rotaxanes have been isolated by preparative chiral stationary phase HPLC separation of a racemic mixture.[4] In addition, Lacour et al. attempted the diastereoselective synthesis of an inherently chiral pseudorotaxane, achieving a de of <8%.[7] Thus, the goal of efficiently synthesizing and investigating the asymmetric induction properties of planar chiral rotaxanes, especially ones with no other element of chirality, remains a major challenge.

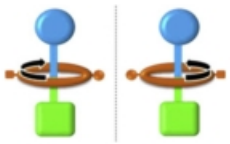

Fig. 1. Mechanical planar chirality in rotaxanes.

Recently, Leigh and co-workers pioneered the use of the active-template metal strategy as an efficient way of synthesising interlocked molecules.[8] The active-metal template strategy utilises the metal to play a dual role of template for entwining or threading the components and as a catalyst for covalent bond formation for capturing the final interlocked product. For rotaxane formation, the macrocycle thus acts as a ligand to coordinate a metal, which in turn acts as a catalyst to mediate the covalent bond formation between two half-threads in the cavity of the macrocycle, leading to a rotaxane (Scheme 1). The use of a metal–ligand complex in such a way opens the possibility of combining asymmetric catalysis with rotaxane bond formation.

* Corresponding author. E-mail address: A.Lee@hw.ac.uk (A.-L. Lee).

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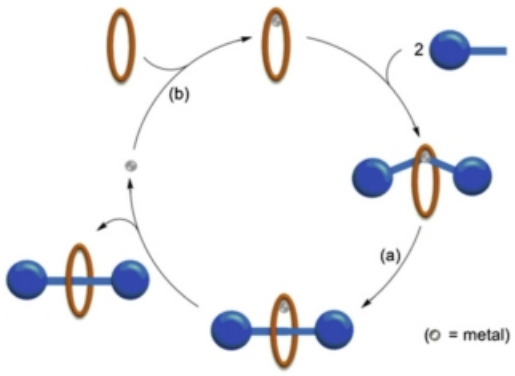
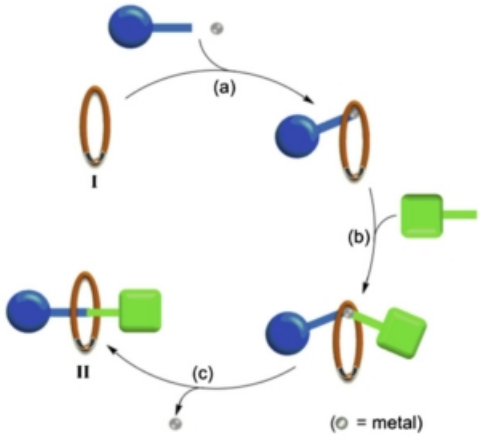
http://dx.doi.org/10.1016/j.tet.2012.10.069



Scheme 1. Active-metal template strategy for forming rotaxanes. (a) Metal-catalyzed covalent bond formation. (b) Metal template turnover in catalytic active-metal template synthesis of rotaxanes.

To this end, we were interested in investigating an asymmetric active-template method to form planar chiral rotaxanes (Scheme 2). If a cross-coupling reaction of two distinct half-threads is used with a macrocycle that lacks any element of symmetry (i.e., C_1-symmetric), and the faces of the metal macrocycle complex are designed to be sterically different (e.g., by having point chirality), the approach of the first fragment should be selectively from the less sterically hindered face of the macrocycle. Approach of the second fragment from the opposite face followed by the metal-catalysed bond formation to form the [2]rotaxane should lead to an optically active, planar chiral rotaxane. If the point chirality within the macrocycle is then removed, the resulting rotaxane will be left solely with mechanical planar chirality.



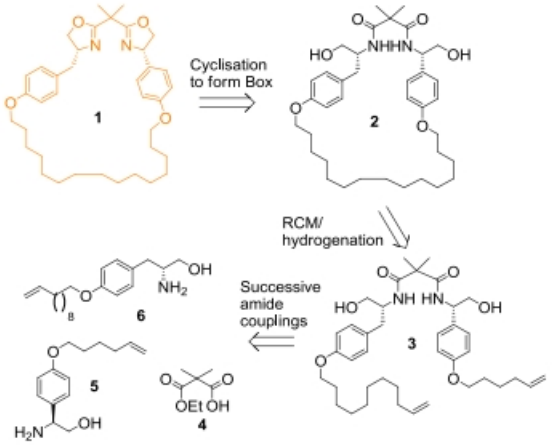
Scheme 2. Proposed asymmetric active-metal template for rotaxane formation. (a) Approach of first fragment to less sterically hindered face of asymmetric macrocycle **I**. (b) Approach of second fragment to opposite face. (c) Covalent bond-forming reaction and demetallation to furnish chiral rotaxane **II**.

In this article, we present the synthesis of the first C_1-symmetric Box macrocycle and its application, along with other model C_1- and C_2-symmetric Box ligands, in the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions as part of our studies towards achieving the active-metal template synthesis of chiral rotaxanes.

2. Results and discussion

2.1. Synthesis of C_1-symmetric Box macrocycle 1

Our first aim was thus to synthesize a suitable C_1-symmetric macrocycle with sterically different faces, which can act as a ligand for various metal-catalyzed reactions, and whose point chirality could be removed after the rotaxane forming process. With this in mind, we chose to synthesize bis-oxazoline (Box) macrocycle **1**.[9] While examples of C_2-symmetric Box macrocycles have been reported by Žinić, Šunjić and co-workers as chiral ligands for Cu-catalyzed reactions,[10] there are no examples of C_1-symmetric Box macrocycles in the literature.[11–15] Our retrosynthetic plan involves ring closing metathesis/hydrogenation of **3** as the key macrocyclisation step, followed by cyclisation of **2** to the bis-oxazoline (Scheme 3). The unsymmetrical fragment **3** will in turn be assembled through successive amide couplings of dimethyl malonic acid monomethylester **4** with amino alcohols **5** and **6**.

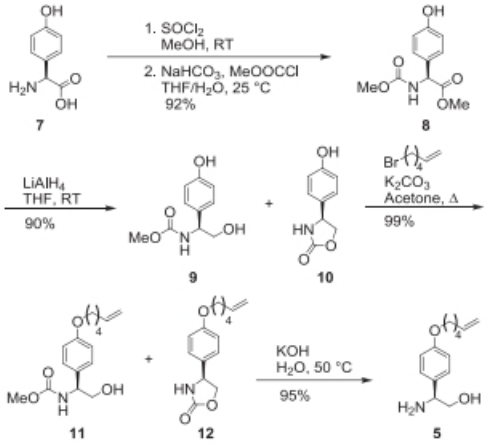


Scheme 3. Retrosynthetic analysis of macrocycle **1**.

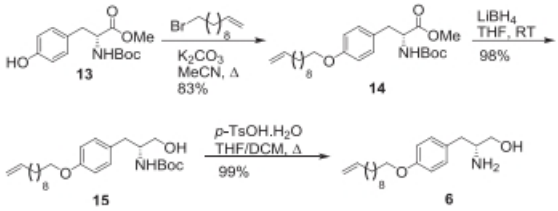
Amino alcohol **5** was prepared as outlined in Scheme 4. Esterification followed by N-protection of 4-hydroxy-L-phenylglycine **7** furnished **8** in high yield (92%). Reduction of ester **8** with $LiAlH_4$ afforded both alcohol **9** as expected, but also oxazolidinone **10**, resulting from reaction between the alcohol and carbamate protecting group. As both products **9** and **10** can be taken forward in the synthetic scheme both were alkylated with 6-bromo-1-hexene under standard conditions to yield ethers **11** and **12**. A mixture of these ethers was then subjected to basic conditions in order to attain amino alcohol **5** in excellent yield (95%).

Synthesis of the other amino alcohol portion **6** began with the alkylation of Boc-D-tyrosine methyl ester **13** with 11-bromoundecene to provide ether **14** in an 83% yield (Scheme 5). Alcohol **15** was produced by reduction of **14** with $LiBH_4$ (98%). Subsequent deprotection of the Boc group gave amino alcohol **6** in almost quantitative yield.

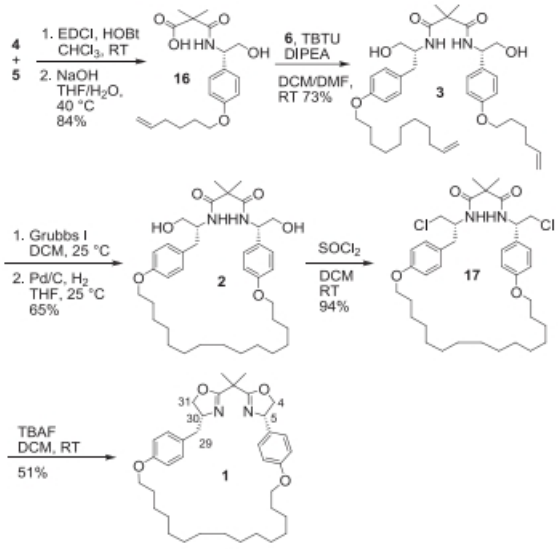
With both amino alcohols in hand, assembly of macrocycle **1** was carried out (Scheme 6). The EDCI-promoted coupling of dimethyl malonic acid monomethylester **4** with amino alcohol **5** followed by hydrolysis afforded amide **16** in an 84% yield. Coupling of amino alcohol **6** with **16**, in a TBTU-promoted reaction, provided unsymmetrical diene **3** in a 73% yield. Treatment of diene **3** with Grubbs' first generation catalyst under high dilution conditions and



Scheme 4. Synthesis of amino alcohol **5**.



Scheme 5. Synthesis of amino alcohol **6**.



Scheme 6. Synthesis of macrocycle **1**.

subsequent reduction of the alkene with Pd/C under a hydrogen atmosphere furnished macrocycle **2** in a good 65% yield over two steps. Finally, Box macrocycle **1** was synthesized from bis-amide **2** in two steps. Reaction of diol **2** with thionyl chloride gave dichloride **17** in high yield (94%). Cyclisation to the Box macrocycle **1** was then achieved by treatment of **17** with TBAF.[16] At this point, we discovered that the Box macrocycle **1** is unstable to silica gel chromatography, forming decomposition products as well as reverting to the uncyclised **2**. Eventually, alumina chromatography techniques were developed for successful purification of **1**. Thus, the synthesis of the first C_1-symmetric bis-oxazoline macrocycle **1** was achieved in a gram scale.

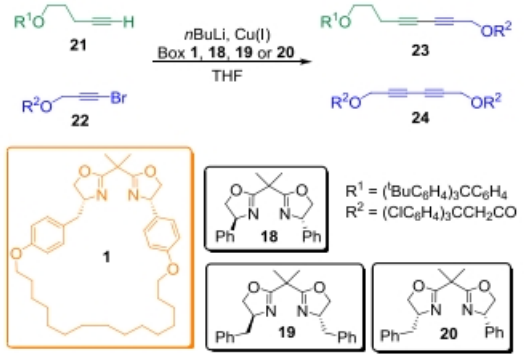
2.2. Catalysis studies

Following the successful synthesis of macrocycle **1**, we set out to study the applicability of Box ligands in the Cadiot–Chodkiewicz,[17] oxidative Heck[18] and CuAAC 'click'[19] reactions as these reactions have been shown to perform well in the active-template synthesis of rotaxanes, and are suitable for heterocoupling of two different half-threads, required to form a dissymmetric thread.[20–22,23] However, since only pyridine and/or bipyridine-based macrocycles have been utilized in these rotaxane forming reactions, and Box ligands have either not been evaluated (Cadiot–Chodkiewicz, CuAAC) or have only seen limited study (oxidative Heck),[24] it was necessary for us to carry out model studies in order to understand how bis-oxazoline ligands will perform for these reactions. Thus, non-macrocyclic C_2-Box ligands **18** and **19**, model C_1-Box ligand **20** as well as macrocycle **1** were utilized in these investigations for comparison purposes between macrocyclic/non-macrocyclic/C_1/C_2 ligands.

In order to emphasize the asymmetry of any planar chiral rotaxanes produced, half-threads with significantly different stopper groups were utilized in our studies. In the Cu(I)-catalysed Cadiot–Chodkiewicz alkyne cross-coupling reaction, stopper fragments **21** and **22** were employed. When the reaction was carried out with C_2-Box ligand **18** (Table 1, entry 1), heterocoupled thread **23** was obtained, along with homocoupled product **24** in a 74:26 ratio and with a 74% conversion from bromoalkyne **22**. With this encouraging result in hand, efforts were made to improve the conversion of the reaction. Running the reaction for 5 days and changing the Cu(I) source to CuCl allowed for full conversion of bromoalkyne **22** to threads **23** and **24** without a change in the heterocoupled:homocoupled thread ratio (Table 1, entry 2).

Once we had our optimised conditions for the reaction using C_2-Box ligand **18**, we turned our attention to model C_1-Box ligand **20** and C_1-macrocycle **1** (Table 1, entries 3 and 4). To our surprise, neither of the reactions gave any indication of either heterocoupled thread **23** or homocoupled bromide **24**. As a control reaction run in the absence of any ligand (Table 1, entry 5) gives us a conversion to heterocoupled thread **23** of 34%, it would appear that the non-macrocycle C_1-Box ligand **20** and C_1-macrocycle **1** are actually *inhibiting* the reaction. This is in direct contrast with C_2-Box ligand **18**, which promotes the reaction to complete conversion. There are two possible causes for this outcome. Either the benzyl (vs Ph) group is inhibiting the reaction or the steric hindrance of having both groups on the same face of the ligand is too great for the reaction to occur. To ascertain the cause, the reaction was carried out with commercially available C_2-symmetric *dibenzyl* Box ligand **19** (Table 1, entry 6). The conversion of bromoalkyne **22** to thread **23** was significantly lower for the dibenzyl Box ligand **19** than for the diphenyl Box compound **18** (22% vs 100%) and was also lower than for the ligand-free reaction (22% vs 34%). This would imply that the dibenzyl Box ligand **19** actively inhibits the Cadiot–Chodkiewicz reaction. It would appear, therefore, that the presence of a benzyl group in conjunction with the C_1-nature of the ligand, with its steric crowding of one face of the compound, completely prevents the

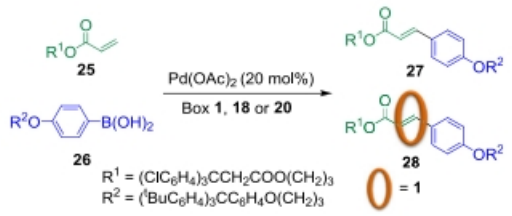
Table 1
Optimization studies for the Cadiot–Chodkiewicz reaction



Entry	Cu(I)	Box	Time	Conv. of **22** to **23**+**24**[a] (%)	Ratio **23**/**24**[a]
1	CuI	**18**	24 h	74	74:26
2	CuCl	**18**	5 days	100	74:26
3	CuCl	**20**	5 days	0	—
4	CuCl	**1**	5 days	0	—
5	CuCl	—	5 days	34	100:0
6	CuCl	**19**	5 days	22	100:0

[a] Determined by ^{1}H NMR spectroscopic analysis of the reaction mixture.

Table 2
Optimization studies for the oxidative Heck reaction



Entry	Box	$Pd(OAc)_2$[a] (%)	Oxidant	Solvent	Conv. of **25** to **27**[b] (%)
1	**18**	20	BQ	$DMF/CHCl_3$	100
2	**20**	20	BQ	$DMF/CHCl_3$	59
3	**20**	20	BQ/O_2	$DMF/CHCl_3$	100
4	—	20	BQ/O_2	$DMF/CHCl_3$	24
5	**1**	20	BQ/O_2	$DMF/CHCl_3$	21
6	**1**	100	—	$DMF/CHCl_3$	50[c]
7	—	100	BQ/O_2	$DMF/CHCl_3$	47
8	—	20	BQ/O_2	$CHCl_3$	31
9	**20**	20	BQ/O_2	$CHCl_3$	20
10	**1**	20	BQ/O_2	$CHCl_3$	5

BQ=benzoquinone.
[a] With respect to alkene **25**.
[b] Determined by ^{1}H NMR spectroscopic analysis of the reaction mixture.
[c] No evidence of rotaxane **28** by mass spectrometry.

Cadiot–Chodkiewicz reaction from occurring in the presence of Box ligand **20** and macrocycle **1**.

Our investigation into the compatibility of Box ligands in reactions known for active-metal template synthesis of rotaxanes continued with the study into Pd(II) oxidative Heck reactions. Reports of bis-oxazolines as ligands for oxidative Heck reactions are limited to only a couple of rare examples as part of ligand screens,[23] so once again, model studies had to be carried out.

Alkene **25** and boronic acid **26** were employed in the oxidative Heck reactions to synthesise **27** as the unsymmetrical thread (Table 2). To our delight, complete conversion of alkene stopper fragment **25** to thread **27** was obtained when the reaction was carried out with benzoquinone as the oxidant in 1:1 $DMF/CHCl_3$, as the components of the reaction were not soluble in DMF alone (Table 2, entry 1). When the ligand was changed from C_2-Box ligand **18** to C_1-Box ligand **20** a lower than expected conversion of 59% was obtained (Table 2, entry 2). However, running the reaction under an oxygen atmosphere (Table 2, entry 3) successfully promotes complete conversion to thread **27**. Comparison with a ligand-free control reaction (Table 2, entry 4) confirms that the non-macrocyclic Box ligands **18** and **20** accelerate the reaction under these conditions.

Encouraged by the complete conversion of alkene **25** to thread **27** by the non-macrocyclic C_1-Box ligand **20**, the synthesis of rotaxane **28** was attempted. However, a conversion to non-interlocked thread **27** of only 21% was achieved (Table 2, entry 5), similar to that of the ligand-free reaction (Table 2, entry 4). It is also in the region of what would be expected if the palladium catalyst was not turning over in the reaction (20%). Therefore, the reaction was repeated with stoichiometric amounts of $Pd(OAc)_2$ in order to determine if the macrocycle was sequestering the palladium and preventing turnover (Table 2, entry 6). The conversion of alkene **25** to non-interlocked thread **27** achieved under these conditions was only 50%, similar to the conversion obtained from the ligand-free stoichiometric control reaction (Table 2, entry 7, 47%). This similarity, when coupled with the lack of rotaxane **28** in the reaction, implies that the Box macrocycle **1** is not bound to the palladium throughout the reaction and only the background reaction is being observed.

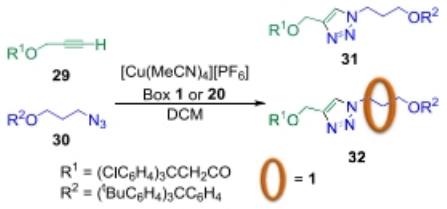
Suspecting competition between the macrocycle **1** and DMF in ligating to the palladium catalyst, the reaction was repeated in chloroform alone as this has a lower binding affinity to transition metals than DMF.[25] A ligand-free control reaction indicated that chloroform was a suitable solvent for the oxidative Heck reaction between alkene **25** and boronic acid **26**, achieving a better conversion than the ligand-free control in $DMF/CHCl_3$, though still quite low at 31% (Table 2, entry 8). When the reaction was carried out with non-macrocyclic C_1-Box ligand **20** and macrocycle **1** (Table 2, entries 9 and 10) the conversions were lower than those obtained in the control reaction; 20% and 5%, respectively. It is apparent from these results that both the non-macrocyclic Box ligand **20** and macrocycle **1** are ligated to the metal catalyst throughout the reaction and are slowing down the reaction compared to the ligand-free control. This supports our conjecture that the DMF is competing with the Box macrocycle in ligating with the palladium. It would appear from our results that there is a series in binding affinity to palladium between the solvent and Box ligands, which runs as follows: non-macrocyclic C_2-Box 18 ~ non-macrocyclic C_1-Box 20<DMF<Box macrocycle **1**.

With the failure to form rotaxane **28**, we turned to investigate the third known active-metal template reaction for compatibility with Box ligands: the CuAAC 'click' reaction of an azide with an acetylene. The reaction is known to work well with bipyridine macrocycles[19] but there are no known examples for the use of bis-oxazoline ligands.

Pleasingly, complete reaction of acetylene **29** with azide **30** was observed at 80 °C[20b] to form triazole thread **31** using model C_1-Box ligand **20** (Table 3, entry 1). Substituting **20** with our macrocycle **1** under the same conditions also resulted in full conversion of acetylene **29**, but disappointingly there was no evidence of rotaxane **32** in either ^{1}H NMR spectroscopy or mass spectrometry. We speculated that the macrocycle may no longer be bound to the copper species at the high temperatures used in the reaction (80 °C). We therefore decided to optimise the CuAAC reaction at room temperature. Unfortunately, initial attempts to optimise the reaction proved irreproducible. The unreliability of the reaction turned out to be related to the concentration, which was subject to change through evaporation of the DCM solvent over the long period of the reaction. The

reactions were therefore carried out in a sealed vial instead, which proves that concentration is key to the observing reactivity (Table 3, entries 3 and 4). Complete conversion of acetylene **29** to thread **31** was achieved in only 48 h through further concentration of the reaction mixture and with the use of additional azide **30** as this was found to be a limiting factor (Table 3, entry 5).

Table 3
Optimization studies for CuAAC click reaction



Entry	Box	Temp (°C)	Concn[a] (mM)	Time	Conv. of **29** to **31**[b] (%)
1	**20**	80[c]	10	68 h	100
2	**1**	80[c]	10	72 h	100[d]
3	**20**	25	10	7 days	0
4	**20**	25	60	4 days	40
5[e]	**20**	25	400	48 h	100
6[e]	**1**	25	400	48 h	100[f]
7[e]	—	25	400	19 h	100

[a] With respect to Box.
[b] Determined by ^{1}H NMR spectroscopic analysis of the reaction mixture.
[c] Reaction carried out in a sealed vessel.
[d] No evidence of rotaxane **32** by mass spectrometry.
[e] With 1.5 equiv azide **30**.
[f] Trace amounts of rotaxane **32** detected by mass spectrometry.

Finally, rotaxane synthesis using macrocycle **1** was attempted again, using the optimised RT conditions and full conversion of acetylene **29** was achieved (Table 3, entry 6). Regrettably, however, rotaxane **32** remained elusive; although detected by mass spectrometry, it was present in only trace amounts. The most likely explanation for the lack of rotaxane, that the Box ligands are not in fact bound to the metal throughout the reaction, is refuted by the result of the ligand-free control reaction (Table 3, entry 7). Like Leigh and co-workers,[22b] we found that the ligand-free reaction reached complete conversion of acetylene **29** into non-interlocked thread **31** in only 19 h, compared to the 48 h required for the reactions with the bis-oxazoline ligands. The Box ligands must inhibit the reaction in some fashion, possibly, as postulated by Leigh et al.,[22b] by preventing a faster, ligand-free pathway for the reaction. The lack of rotaxane in our CuAAC 'click' reaction with macrocycle **1** must therefore be due to some hindrance in carrying out the reaction *through* the macrocycle cavity, with only a small percentage of the thread being formed within the cavity. Redesign of the Box macrocycle **1** to provide a more rigid structure may be necessary for the successful asymmetric synthesis of planar chiral rotaxanes via the active-template method.

3. Conclusions

The synthesis of the first C_1-symmetric bis-oxazoline macrocycle **1** was successfully achieved in gram scale. Macrocycle **1**, along with model C_2 bis-oxazoline ligands **18** and **19**, and C_1-Box ligand **20** were investigated as ligands for the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions. This study constitutes the first report of Cadiot–Chodkiewicz and CuAAC 'click' reactions using Box ligands, as well as the first dedicated study of oxidative Heck reactions using Box ligands. In the Cadiot–Chodkiewicz reaction, C_2-Box ligand **18** successfully promotes the reaction to completion, but in contrast, C_1-Box ligands **20** and **1** surprisingly inhibit the reaction. Pd(II)-catalysed oxidative Heck reaction with Box macrocycle **1** succeeds in forming the coupled thread **27**, but not the rotaxane **28**. Our investigations suggest that DMF competes with Box macrocycle **1** as a ligand for Pd under oxidative Heck conditions. The CuAAC reaction with Box ligands **20** and **1** once again successfully forms the non-interlocked thread **31** under mild conditions, but the desired rotaxane was formed in only trace quantities. Control studies suggest that the macrocycle ligand **1** is bound to the metal during the CuAAC reaction, making it the most promising reaction of the three investigated, although a more rigid macrocycle design is probably necessary for successful rotaxane formation in the future. Although macrocycle **1** proved unsuitable for our ultimate aim of synthesizing mechanically planar chiral rotaxanes, the results of our model studies nevertheless provide valuable insight into the behaviour of C_1 and C_2 bis-oxazolines as ligands in these copper- and palladium-catalyzed reactions.

4. Experimental

4.1. General experimental section

Unless otherwise stated, all reactions were performed under nitrogen atmosphere. ^{1}H NMR spectra were recorded on Bruker AC200, AV 300, DPX 400 and AV 400 spectrometers at 200, 300 and 400 MHz, respectively, and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 50, 75 and 101 MHz, respectively. Chemical shifts (δ in parts per million) were referenced to tetramethylsilane (TMS) or to residual solvent peaks. *J* values are given in Hertz and s, d, dd, dt, ddt, t, tdd, quin. and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, triplet, triplet of doublet of doublet, quintet and multiplet. The numbers for the peak assignment of macrocycle **1** are referred to the system in Scheme 6. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin–Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution onto a diamond/ZnSe plate. Optical rotations were recorded on a Bellingham & Stanley ADP410 polarimeter. Starting compounds 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **4**,[26] 4,4′,4″-((4-(pent-4-ynyloxy) phenyl)methanetriyl)tris(*tert*-butyl benzene) **21**,[27] 4-(3-(4-(tris(4-*tert*-butyl-phenyl)methyl)phenoxy) propoxy)phenylboronic acid **26**,[21] 1-(3-azido-propoxy)-4-(tris-(4-*tert*-butyl-phenyl)-methyl)-benzene **30**[22a] and (*S*)-3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid **33**[11d] were synthesized according to literature procedures. All other reagents used were purchased from commercial suppliers and were used without any further purification unless otherwise stated. *N*-Bromosuccinimide (NBS) was recrystallised from water. Dichloromethane (DCM) was distilled over CaH_2 and stored over 4 Å molecular sieves. Acetone was stored over 3 Å sieves. Tetrahydrofuran (THF) was dried by distillation from sodium-benzophenone under nitrogen. Anhydrous *N*,*N* dimethylformamide (DMF) was used as supplied (Sureseal®). Petrol ether refers to petroleum ether (40–60). All glassware was heat gun dried. Flash column chromatography, unless otherwise stated, was carried out using Matrix silica gel 60 from Fisher Chemicals. Alumina flash column chromatography was carried out using activated neutral aluminium oxide Brockmann I 150 mesh from Aldrich. TLC was performed using Merck silica gel 60 F254 precoated sheets and visualized by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate.

*4.1.1. (S)-Methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino) acetate (**8**).* Thionyl chloride (41.0 mL, 560 mmol) was added dropwise to a stirring solution of (*S*)-2-amino-2-(4-hydroxyphenyl)

acetic acid **7** (52.5 g, 310 mmol) in methanol (1.1 L). The resulting mixture was stirred at 25 °C for 16 h. The reaction was concentrated under reduced pressure and the resulting residue washed with diethyl ether. The resulting crude product was dissolved in 1:1 THF/H_2O (1 L) and $NaHCO_3$ (79 g, 940 mmol) added. Methyl chloroformate (26.6 mL, 340 mmol) was added dropwise and the resulting mixture stirred at 25 °C for 16 h. The reaction was quenched with water (500 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was recrystallised from ethyl acetate/hexane to yield the title compound **8** (68.8 g, 92%) as a white solid. Mp 138–139 °C; R_f 0.29 (1:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +153.5 (*c* 0.99, MeOH); ν_{max}/cm^{-1} 3371 (NH), 3279 br (OH), 3000 (CH), 2951 (CH), 2845 (CH), 1756 (C=O), 1698 (C=O), 1616 (Ar C=C), 1598 (Ar C=C), 1510 (Ar C=C), 1440 (Ar C=C), 1264 (N–CO–O), 1213 (C–OH), 1171 (Ar CH), 1059 (N–CO–O), 1011 (C–OH), 780 (Ar CH); δ_H (200 MHz, C_2D_6SO) 8.00 (1H, d, *J* 7.5, N*H*), 7.29–7.04 (2H, m, Ar–*H*), 6.79–6.60 (2H, m, Ar–*H*), 5.08 (1H, d, *J* 7.5, *CH*COOMe), 3.60 (3H, s, OCH_3), 3.55 (3H, s, OCH_3); δ_C (50 MHz, C_2D_6SO) 171.8 (*C*), 157.4 (*C*), 156.5 (*C*), 129.1 (CH), 126.4 (*C*), 115.3 (CH), 57.5 (*C*H), 52.1 (*C*H_3), 51.6 (*C*H_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{14}NO_5$ 240.0866, found 240.0869.

*4.1.2. (S)-Methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate (**9**).* $LiAlH_4$ (7.60 g, 200 mmol) was added portionwise to a stirring solution of (*S*)-methyl 2-(4-hydroxyphenyl)-2-((methoxycarbonyl) amino)acetate **8** (24.0 g, 100 mmol) in THF (1.5 L) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h then warmed to RT over 24 h. The reaction was cooled to 0 °C and ice-cold water (16 mL) added. The mixture was stirred at 0 °C for 10 min then 15% aq NaOH (16 mL) was added and the reaction stirred at 0 °C for a further 10 min. Ice-cold water (48 mL) was added and the reaction stirred at 0 °C for 30 min. The resulting suspension was filtered and the filtrate dried ($MgSO_4$) then concentrated under reduced pressure. The resulting residue was purified by column chromatography (petrol ether to 1:1 petrol ether/ethyl acetate to ethyl acetate) to yield the title compound **9** (12.7 g, 60%) as a white solid. Mp 112–115 °C; R_f 0.20 (2:1 ethyl acetate/petrol ether); $[\alpha]_D^{18}$ +70.6 (*c* 1.02, MeOH); ν_{max}/cm^{-1} 3339 (OH/NH), 2944 (CH), 1685 (C=O), 1600 (NH), 1534 (Ar C=C), 1517 (Ar C=C), 1452 (Ar C=C), 1360 (OH), 1218 (Ar C–O), 1173 (N–CO–O), 1058 (N–CO–O), 1013 (C–O); δ_H (300 MHz, C_2D_6SO) 7.40 (1H, d, *J* 8.1, N*H*), 7.13–7.03 (2H, m, Ar–*H*), 6.78–6.53 (2H, m, Ar–*H*), 4.75 (1H, t, *J* 5.5, O*H*), 4.46 (1H, dt, *J* 8.1, 6.2, *CH*CH_2OH), 3.50 (3H, s, OCH_3), 3.44 (2H, t, *J* 6.2, CHCH_2OH); δ_C (75 MHz, C_2D_6SO) 156.8 (*C*), 156.7 (*C*), 132.1 (*C*), 128.3 (CH), 115.2 (*C*H), 65.3 (*C*H_2), 57.0 (*C*H), 51.6 (*C*H_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{10}H_{14}NO_4$ 212.0917, found 212.0919.

*4.1.3. (S)-4-(4-Hydroxyphenyl)oxazolidin-2-one (**10**).*[28] Compound **10** was also formed as a side-product (5.40 g, 30%) as a white solid. Mp 203–205 °C [lit.[28] mp 201–204 °C]; R_f 0.32 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +48.6 (*c* 1.48, MeOH) [lit.[28] $[\alpha]_D^{20}$ +41.4 (*c* 1.70, EtOH)]; ν_{max}/cm^{-1} 3304 (NH), 3226 br (OH), 2925 (CH), 2833 (CH), 1724 (C=O), 1614 (Ar C=C), 1601 (NH), 1513 (Ar C=C), 1487 (Ar C=C), 1374 (OH), 1238 (N–CO–O), 1212 (C–O), 1029 (N–CO–O), 825 (Ar CH); δ_H (300 MHz, C_2D_6SO) 8.04 (1H, s, N*H*), 7.19–7.09 (2H, m, Ar–*H*), 6.82–6.72 (2H, m, Ar–*H*), 4.81 (1H, dd, *J* 8.6, 7.0, CHC*H*HO), 4.60 (1H, dd, *J* 8.6, 8.6, *CH*CHHO), 3.95 (1H, dd, *J* 8.6, 7.0, CHCH*H*O); δ_C (75 MHz, C_2D_6SO) 158.9 (*C*), 157.2 (*C*), 131.0 (*C*), 127.4 (CH), 115.4 (CH), 71.6 (*C*H_2), 54.8 (CH); HRMS (ESI) $[M+H]^+$ calcd for $C_9H_{10}NO_3$ 180.0655, found 180.0654.

*4.1.4. (S)-Methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethyl carbamate (**11**).* 6-Bromohex-1-ene (5.00 mL, 37.7 mmol) was added dropwise to a stirring suspension of (*S*)-methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate **9** (7.42 g, 35.1 mmol) and K_2CO_3 (5.36 g, 38.8 mmol) in acetone (80 mL). The resulting mixture was heated at reflux for 43 h. After cooling, the reaction was quenched with water (80 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 9:1 ethyl acetate/petrol ether) to yield the title compound **11** (6.94 g, 68%) as a white solid. Mp 73–74 °C; R_f 0.48 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +64.0 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3337 br (OH, NH), 2945 (CH), 2867 (CH), 1692 (C=O), 1641 (C=C), 1613 (Ar C=C), 1586 (Ar C=C), 1533 (NH), 1513 (Ar C=C), 1478 (Ar C=C), 1460 (OH), 1265 (N–CO–O), 1241 br (C–O–C), 1178 (Ar CH), 1114 (C–O–C), 1089 (C–O), 1056 (N–CO–O), 1030 (C–OH), 997 (=CH), 915 (=CH), 825 (Ar CH), 779 (OH); δ_H (200 MHz, $CDCl_3$) 7.25–7.16 (2H, m, Ar–*H*), 6.96–6.72 (2H, m, Ar–*H*), 5.83 (1H, ddt, *J* 17.0, 10.4, 6.6, *CH*=CH_2), 5.37 (1H, d, *J* 7.1, N*H*), 5.11–4.92 (2H, m, =*C*H_2), 4.77 (1H, dd, *J* 7.1, 5.4, *CH*CH_2OH), 3.95 (2H, t, *J* 6.2, OCH_2), 3.84 (2H, t, *J* 5.4, CHCH_2OH), 3.68 (3H, s, OCH_3), 2.31–2.04 (3H, m, alkyl-H, O*H*), 1.90–1.69 (2H, m, alkyl-*H*), 1.68–1.46 (2H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 158.8 (*C*), 157.1 (*C*), 138.5 (*C*H), 130.9 (*C*), 127.7 (CH), 114.8 (*C*H and *C*H_2 overlapping), 67.8 (*C*H_2), 66.6 (*C*H_2), 56.6 (CH), 52.4 (*C*H_3), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.3 (*C*H_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{24}NO_4$ 294.1700, found 294.1703.

Cyclic compound **12** was also formed as a side-product (2.83 g, 32%) as a white solid. Mp 96–97 °C; R_f 0.68 (2:1 ethyl acetate/petrol ether); $[\alpha]_D^{22}$ +28.6 (*c* 0.14, $CHCl_3$); ν_{max}/cm^{-1} 3233 (NH), 3139 (Ar CH), 2936 (CH), 2921 (CH), 1740 (C=O), 1640 (Ar C=C), 1614 (NH), 1586 (Ar C=C), 1512 (Ar C=C), 1393 (=CH), 1239 (C–O), 1061 (C–O), 1025 (N–CO–O), 925 (=CH), 828 (Ar CH); δ_H (200 MHz, $CDCl_3$) 7.33–7.21 (2H, m, Ar–*H*), 6.98–6.85 (2H, m, Ar–*H*), 5.84 (1H, ddt, *J* 17.0, 10.0, 6.6, *CH*=CH_2), 5.50 (1H, s, N*H*), 5.14–4.84 (3H, m, CH*CH*HO, =*C*H_2), 4.67 (1H, dd, *J* 8.3, 8.3, CHCH*H*O), 4.17 (1H, dd, *J* 8.3, 7.1, *CH*CH_2O), 3.97 (2H, t, *J* 6.4, OCH_2CH_2), 2.16–2.04 (2H, m, alkyl-*H*), 1.90–1.72 (2H, m, alkyl-*H*), 1.61–1.48 (2H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 159.5 (*C*), 138.4 (*C*), 131.0 (*C*), 127.4 (2×*C*H overlapping), 115.0 (CH), 114.8 (*C*H_2), 72.7 (*C*H_2), 67.9 (*C*H_2), 55.9 (CH), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.2 (*C*H_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1438, found 262.1441.

*4.1.5. (S)-2-Amino-2-(4-(hex-5-enyloxy)phenyl)ethanol (**5**).* A suspension of (*S*)-methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate **11** (8.71 g, 29.7 mmol) and (*S*)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one **12** (2.86 g, 10.9 mmol) in a solution of KOH (25% aq, 365 mL) was stirred at 50 °C for 27 h. After cooling, the reaction was quenched with water (365 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **5** (9.12 g, 95%) as a pale yellow solid. Mp 72–73 °C; R_f 0.03 (20:1 DCM/methanol); $[\alpha]_D^{20}$ +28.3 (*c* 1.27, $CHCl_3$); ν_{max}/cm^{-1} 3500 br (OH), 3323 (NH), 3067 (Ar CH), 2936 (CH), 2865 (CH), 1713 (Ar C–H), 1642 br (C=C, NH_2), 1611 (Ar C=C), 1559 (Ar C=C), 1512 (Ar C=C), 1469 (Ar C=C), 1389 (C–N), 1245 (C–O–C), 1176 (C–N), 1155 (C–N), 1065 (Ar CH), 1028 (C–OH), 993 (=CH), 907 (=CH), 827 (Ar CH, NH_2), 809 (NH_2); δ_H (200 MHz, $CDCl_3$) 7.26–7.19 (2H, m, Ar–*H*), 6.97–6.70 (2H, m, Ar–*H*), 6.00–5.68 (1H, m, *CH*=CH_2), 5.14–4.84 (2H, m, =*C*H_2), 4.09–3.84 (3H, m, OCH_2, *CH*CH_2O), 3.69 (1H, dd, *J* 10.8, 4.6, CHC*H*HOH), 3.52 (1H, dd, *J* 10.8, 8.3, CHCH*H*OH), 2.40 (3H, s, NH_2, O*H*), 2.22–2.00 (2H, m, alkyl-*H*), 1.91–1.69 (2H, m, alkyl-*H*), 1.68–1.39 (2H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 158.4 (*C*), 138.5 (CH), 134.4 (*C*), 127.5 (*C*H), 114.7 (*C*H), 114.5 (*C*H_2), 67.9 (*C*H_2), 67.7 (*C*H_2), 56.7 (CH), 33.4 (*C*H_2), 28.6 (*C*H_2), 25.2 (*C*H_2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{21}NNaO_2$ 258.1465, found 258.1467.

*4.1.6. (R)-Methyl 2-(tert-butoxycarbonylamino)-3-(4-(undec-10-enyloxy)phenyl)propanoate (**14**).* A solution of 11-bromoundec-1-ene (53.4 g, 230 mmol) in acetonitrile (100 mL) was added

dropwise to a stirring suspension of (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate **13** (56.4 g, 190 mmol) and K_2CO_3 (32.0 g, 230 mmol) in acetonitrile (250 mL). The resulting mixture was heated at reflux for 18 h. After cooling, the reaction was quenched with water (500 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petrol ether to 4:1 petrol ether/ethyl acetate) then recrystallised from toluene/petrol ether to yield the title compound **14** (70.8 g, 83%) as a white solid. Mp 59–62 °C; R_f 0.30 (9:1 petrol ether/ethyl acetate); $[\alpha]_D^{20}$ −33.9 (*c* 1.12, $CHCl_3$); ν_{max}/cm^{-1} 3367 (NH), 2980 (Ar CH), 2920 (CH), 2851 (CH), 1737 (C=O), 1691 (C=O), 1641 (C=C), 1614 (Ar C=C), 1583 (NH), 1524 (Ar C=C), 1512 (Ar C=C), 1467 (CH), 1367 (CH), 1242 (C–O–C), 1161 (C–O–C/N–CO–O) 994 (=CH), 909 (=CH), 826 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.08–6.99 (2H, m, Ar–*H*), 6.89–6.77 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 16.9, 10.3, 6.6, C*H*=CH_2), 5.06–4.90 (3H, m, =CH_2, N*H*), 4.61–4.46 (1H, m, *CH*COOMe), 3.93 (2H, t, *J* 6.6, OCH_2), 3.72 (3H, s, OCH_3), 3.11–2.92 (2H, m, CH_2CHCO), 2.11–1.98 (2H, m, alkyl-*H*), 1.84–1.68 (2H, m, alkyl-*H*), 1.51–1.25 (21H, m, alkyl-H, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 172.4 (*C*), 158.2 (*C*), 154.9 (*C*), 139.2 (CH), 130.2 (CH), 127.7 (*C*), 114.5 (CH), 114.1 (CH_2), 79.9 (*C*), 68.0 (CH_2), 54.5 (CH), 52.2 (CH_3), 37.5 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2) (plus two overlapping peaks), 28.3 (CH_3), 26.0 (CH_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{26}H_{42}NO_5$ 448.3057, found 448.3053.

*4.1.7. (R)-tert-Butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl) propan-2-ylcarbamate (**15**).* $LiBH_4$ (5.90 g, 270 mmol) was added portionwise to a stirring solution of (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(undec-10-en-1-yloxy)phenyl)propanoate **14** (60.4 g, 130 mmol) in THF (1.2 L) at 0 °C. The resulting mixture was allowed to warm to RT over 16 h. The reaction was quenched with 1 M aq HCl until effervescing ceased and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was triturated with ice-cold hexane (2×500 mL) and sonicated briefly. The resulting precipitate was filtered, washed with hexane and dried in vacuo to yield the title compound **15** (55 g, 98%) as a white solid. Mp 67–69 °C; R_f 0.15 (4:1 petrol ether/ethyl acetate); $[\alpha]_D^{22}$ +12.3 (*c* 2.11, $CHCl_3$); ν_{max}/cm^{-1} 3358 br (NH, OH), 2974 (Ar CH), 2920 (CH), 2852 (CH), 1689 (C=O), 1642 (Ar C=C), 1614 (Ar C=C), 1582 (NH), 1528 (Ar C=C), 1510 (Ar C=C), 1268 (N–CO–O), 1241 (C–O–C), 1171 (N–CO–O), 1061 (C–OH), 1035 (C–OH), 1004 (=CH), 906 (=CH); δ_H (300 MHz, $CDCl_3$) 7.16–7.08 (2H, m, Ar–*H*), 6.89–6.80 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 13.2, 10.3, 6.6, C*H*=CH_2), 5.07–4.90 (2H, m, =CH_2), 4.73 (1H, d, *J* 7.7, N*H*), 3.93 (2H, t, *J* 6.6, OCH_2), 3.88–3.72 (1H, m, *CH*CH_2OH), 3.72–3.48 (2H, m, CH_2OH), 2.78 (2H, d, *J* 7.3, CH_2CHCH_2), 2.41 (1H, br s, O*H*), 2.11–1.98 (2H, m, alkyl-*H*), 1.85–1.71 (2H, m, alkyl-*H*), 1.52–1.24 (21H, m, alkyl-*H*, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 157.9 (*C*), 156.2 (*C*), 139.2 (CH), 130.1 (CH), 129.4 (*C*), 114.6 (CH), 114.1 (CH_2), 79.7 (*C*), 68.0 (CH_2), 64.4 (CH_2), 53.9 (CH), 36.2 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.9 (CH_2) (plus two overlapping peaks), 28.3 (CH_3), 26.0 (CH_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{42}NO_4$ 420.3108, found 420.3101.

*4.1.8. (R)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol (**6**).* *p*-Toluenesulfonic acid monohydrate (53.9 g, 280 mmol) was added portionwise to a stirring solution of (*R*)-*tert*-butyl 1-hydroxy-3-(4-(undec-10-en-1-yloxy)phenyl)propan-2-ylcarbamate **15** (59.4 g, 140 mmol) in 1:1 THF/H_2O (1.5 L). The resulting mixture was heated at reflux for 18 h. After cooling, the reaction was quenched with 2 M aq NaOH (500 mL) and the aqueous layer extracted with ethyl acetate (250 mL) and then DCM (250 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **6** (44.7 g, 99%) as a white solid. Mp 75–78 °C; R_f 0.03 (9:1 petrol ether/ethyl acetate); $[\alpha]_D^{20}$ +7.7 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1} 3355 (NH), 3298 (NH), 3077 (Ar CH), 2923 br (OH), 2851 (CH), 1613 (Ar C=C), 1582 (Ar C=C), 1509 (Ar C=C), 1467 (Ar C=C), 1243 (C–O–C), 1059 (C–OH), 909 (=CH); δ_H (400 MHz, $CDCl_3$) 7.13–7.03 (2H, m, Ar–*H*), 6.90–6.79 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 17.0, 10.3, 6.7, C*H*=CH_2), 5.06–4.88 (2H, m, =CH_2), 3.93 (2H, t, *J* 6.5, OCH_2), 3.63 (1H, dd, *J* 10.6, 3.2, *CH*HOH), 3.37 (1H, dd, *J* 10.6, 6.5, CH*H*OH), 3.13–3.02 (1H, m, *CH*NH_2), 2.73 (1H, dd, *J* 13.5, 5.3, *CH*HCHNH_2), 2.47 (1H, dd, *J* 13.5, 8.5, CH*H*CHNH_2), 2.24–1.99 (5H, m, alkyl-*H*, NH_2, O*H*), 1.85–1.70 (2H, m, alkyl-*H*), 1.51–1.23 (12H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 157.8 (*C*), 139.2 (*C*H), 130.3 (*C*H), 130.1 (*C*), 114.6 (*C*H), 114.1 (CH_2), 68.0 (CH_2), 66.1 (CH_2), 54.3 (*C*H), 39.8 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2) (plus one overlapping peak), 27.6 (CH_2), 26.0 (CH_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{34}NO_2$ 320.2584, found 320.2588.

*4.1.9. (S)-Ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethy lamino)-2,2-dimethyl-3-oxopropanoate (**34**).* A solution of EDCI (9.50 g, 50.0 mmol) in chloroform (53 mL) was added dropwise to a stirring solution of (*S*)-2-amino-(4-(hex-5-enyloxy)phenyl)ethanol **5** (12.0 g, 50.0 mmol) and HOBt (6.70 g, 50.0 mmol) in chloroform (395 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 h. A solution of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **4** (8.50 g, 45.0 mmol) in chloroform (79 mL) was added dropwise. The resulting mixture was allowed to warm to RT for 18 h. The reaction was quenched with 3 M aq HCl (100 mL) and the aqueous layer extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 petrol ether/ethyl acetate) to yield the title compound **34** (16.0 g, 95%) as a white solid. Mp 73–75 °C; R_f 0.35 (1:1 petrol ether/ethyl acetate); $[\alpha]_D^{19}$ +37.0 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 3309 (NH), 3258 br (OH), 3074 (Ar CH), 2985 (CH), 2939 (CH), 2862 (CH), 1730 (C=O), 1644 (C=O), 1611 (Ar C=C), 1584 (Ar C=C), 1548 (NH), 1511 (Ar C=C), 1477 (Ar C=C), 1265 (C–N), 1246 (C–O–C), 1174 (C–O–C), 1151 (C–O), 1028 (C–OH), 997 (C=C), 917 (C=C), 827 (Ar CH); δ_H (200 MHz, $CDCl_3$) 7.24–7.09 (3H, m, Ar–*H*, N*H*), 6.89–6.78 (2H, m, Ar–*H*), 5.81 (1H, ddt, *J* 17.0, 10.4, 6.6, C*H*=CH_2), 5.10–4.86 (3H, m, *CH*CH_2OH, CH=CH_2), 4.15 (2H, q, *J* 7.1, O$CH_2$$CH_3$), 3.91 (2H, t, *J* 6.4, O$CH_2$$CH_2$), 3.82–3.69 (2H, m, CHC$H_2$OH), 3.47 (1H, s, O*H*), 2.20–1.96 (2H, m, alkyl-*H*), 1.88–1.68 (2H, m, alkyl-*H*), 1.64–1.48 (2H, m, alkyl-*H*), 1.45 (3H, s, CH_3), 1.42 (3H, s, CH_3′), 1.23 (3H, t, *J* 7.1, OCH$_2$$CH_3$); δ_C (50 MHz, $CDCl_3$) 174.6 (*C*), 172.2 (*C*), 158.4 (*C*), 138.3 (CH), 130.8 (*C*), 127.5 (*C*H), 114.6 (CH_2), 114.5 (CH), 67.5 (CH_2), 65.9 (CH_2), 61.5 (CH_2), 55.1 (CH), 49.7 (*C*), 33.2 (CH_2), 28.5 (CH_2), 25.1 (CH_2), 23.4 (2×CH_3 overlapping), 13.8 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{32}NO_5$ 378.2275, found 378.2275.

*4.1.10. (S)-3-(1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid (**16**).* A solution of NaOH (10.6 g, 260 mmol) in 1:1 THF/H_2O (300 mL) was added to a stirring solution of (*S*)-ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoate **34** (10.0 g, 26.0 mmol) in 1:1 THF/H_2O (500 mL). The resulting mixture was stirred at 45 °C for 4 h. The reaction was cooled to 0 °C and quenched with 6 M aq HCl until pH 1 was reached. The mixture was extracted with ethyl acetate and DCM and the combined organic layers were washed with water, brine and dried ($MgSO_4$). The resulting solution was concentrated under reduced pressure to yield the title compound **16** (8.20 g, 89%) as a white solid. Mp 118–121 °C; R_f 0.05 (9:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +73.0 (*c* 1.26, $CHCl_3$); ν_{max}/cm^{-1} 3308 br (OH/NH), 2980 (Ar CH), 2935 (CH), 2865 (CH), 1715 (Ar CH), 1679 (C=O), 1655 (C=O), 1613 (Ar C=C),

1559 (NH), 1512 (Ar C=C), 1466 (Ar C=C), 1389 (C–N), 1247 (C–O–C/C–N), 1175 (C–N), 1156 (C–O), 1028 (C–OH), 992 (=CH), 900 (=CH), 827 (Ar CH), 810 (NH); δ_H (200 MHz, $CDCl_3$) 7.92 (1H, d, *J* 5.8, N*H*), 7.20 (2H, d, *J* 8.3, Ar–*H*), 6.82 (2H, d, *J* 8.3, Ar–*H*), 5.83 (1H, ddt, *J* 16.8, 10.1, 6.6, C*H*=CH$_2$), 5.22–4.92 (3H, m, C*H*CH$_2$OH, =C*H*$_2$), 4.04–3.70 (4H, m, C*H*$_2$OH, OC*H*$_2$), 2.24–2.04 (2H, m, alkyl-*H*), 1.90–1.67 (2H, m, alkyl-*H*), 1.65–1.35 (8H, m, alkyl-*H*); δ_C (50 MHz, $CDCl_3$) 177.2 (*C*), 173.8 (*C*), 158.6 (*C*), 138.5 (CH), 130.6 (*C*), 127.6 (CH), 114.7 (CH$_2$), 114.7 (CH), 67.7 (CH$_2$), 64.8 (CH$_2$), 55.4 (CH), 49.5 (*C*), 33.4 (CH$_2$), 28.6 (CH$_2$), 25.3 (CH$_2$), 23.5 (CH$_3$), 23.4 (CH$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{28}NO_5$ 350.1962, found 350.1965.

*4.1.11. N^1-((S)-1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethyl)-N^3-((R)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide (**3**).* (*R*)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol **6** (4.31 g, 13.5 mmol) was added to a stirring solution of (*S*)-3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid **16** (4.20 g, 12.0 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) (4.30 g, 13.0 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (2.30 mL, 13.4 mmol) in 4:1 DCM/DMF (400 mL). The resulting mixture was stirred at RT for 93 h. The reaction was quenched with water (400 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 95:5 ethyl acetate/methanol) to yield the title compound **3** (5.70 g, 73%) as a white solid. Mp 77–78 °C; R_f 0.47 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +37.9 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 3335 br (OH/NH), 2926 (CH), 2855 (CH), 1640 (C=O), 1613 (Ar C=C), 1583 (NH), 1510 (Ar C=C), 1471 (Ar C=C), 1243 (C–O–C), 1176 (C–O), 1034 (C–OH), 994 (=CH), 909 (=CH), 829 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.22–7.04 (5H, m, Ar–*H*, N*H*), 6.89–6.78 (4H, m, Ar–*H*), 6.65 (1H, d, *J* 7.9, N*H*), 5.89–5.77 (2H, m, C*H*=CH$_2$, C*H*=CH$_2$′), 5.08–4.90 (5H, m, C*H*CH$_2$OH, =C*H*$_2$, =C*H*$_2$′), 4.16–4.05 (1H, m, C*H*(CH$_2$)$_2$), 3.96–3.88 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.85–3.72 (2H, m, C*H*$_2$OH), 3.63 (1H, dd, *J* 11.2, 3.8, CH$_2$CHC*H*HOH), 3.55 (1H, dd, *J* 11.2, 5.6, CH$_2$CHCH*H*OH), 2.94 (2H, br s, O*H*), 2.82 (1H, dd, *J* 13.8, 6.7, C*H*HCHCH$_2$OH), 2.73 (1H, dd, *J* 13.8, 7.6, CH*H*CHCH$_2$OH), 2.18–2.00 (4H, m, alkyl-*H*), 1.84–1.72 (4H, m, alkyl-*H*), 1.61–1.51 (2H, m, alkyl-*H*), 1.49–1.28 (18H, m, C*H*$_3$, C*H*$_3$′, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 158.7 (Ar–*C*), 157.9 (Ar–*C*), 139.2 (*C*H=CH$_2$), 138.5 (*C*H=CH$_2$′), 130.5 (Ar–*C*, Ar–CH), 130.1 (Ar–CH), 129.2 (Ar–*C*), 127.6 (Ar–CH), 114.8 (=CH$_2$), 114.7 (Ar–CH), 114.6 (CH$_2$), 114.1 (Ar–CH), 68.0 (OCH$_2$), 67.8 (OCH$_2$′), 66.2 (CH$_2$OH), 64.0 (CH$_2$CHCH$_2$OH), 55.4 (CHCH$_2$OH), 53.3 (CH(CH$_2$)$_2$), 49.8 (*C*(CH$_3$)$_2$), 35.9 (CH$_2$CHCH$_2$OH), 33.8 (alkyl-CH$_2$), 33.4 (alkyl-CH$_2$), 29.5 (alkyl-CH$_2$), 29.4 (alkyl-CH$_2$), 29.3 (alkyl-CH$_2$), 29.1 (alkyl-CH$_2$), 28.9 (alkyl-CH$_2$) (plus one overlapping peak), 28.7 (alkyl-CH$_2$), 26.0 (alkyl-CH$_2$), 25.3 (alkyl-CH$_2$), 23.8 (CH$_3$), 23.6 (CH$_3$′); HRMS (ESI) $[M+H]^+$ calcd for $C_{39}H_{59}N_2O_6$ 651.4368, found 651.4362.

*4.1.12. Macrocycle **2**.* A solution of N^1-((*S*)-1-(4-(hex-5-enyloxy) phenyl)-2-hydroxyethyl)-N^3-((*R*)-1-hydroxy-3-(4-(undec-10-enyloxy) phenyl)propan-2-yl)-2,2-dimethylmalonamide **3** (2.30 g, 3.53 mmol) in DCM (130 mL) was added dropwise to a stirring solution of Grubbs first generation catalyst (0.29 g, 0.35 mmol) in DCM (930 mL) under an argon atmosphere. The resulting mixture was heated at reflux for 7 days. The reaction was cooled to RT and concentrated under reduced pressure. The resulting residue was passed through a silica column (9:1 petrol ether/ethyl acetate to 5% methanol/ethyl acetate) to remove unreacted **3**. The resulting crude product was dissolved in THF (200 mL) and 10% w/w Pd/C (0.87 g) added. The resulting mixture was placed under a hydrogen atmosphere and stirred at RT for 6 h. The mixture was then flushed through a plug of Celite with THF and the resulting solution concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 5% methanol/ethyl acetate) to yield the title compound **2** (1.42 g, 65%) as a white solid. Mp 186–190 °C; R_f 0.08 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +68.7 (*c* 0.99, $CHCl_3$); ν_{max}/cm^{-1} 3428 (NH), 3368 br (OH), 2924 (CH), 2854 (CH), 1655 (C=O), 1633 (NH), 1611 (Ar C=C), 1582 (Ar C=C), 1530 (N–C=O), 1513 (Ar C=C), 1470 (Ar C=C), 1243 (C–N, C–O–C), 1179 (C–OH), 1073 (C–O–C), 1038 (C–O–C, C–OH), 826 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.16–7.07 (4H, m, Ar–*H*), 6.94 (1H, d, *J* 7.0, N*H*), 6.88–6.81 (4H, m, Ar–*H*), 6.56 (1H, d, *J* 7.9, N*H*), 4.92–4.84 (1H, m, C*H*CH$_2$OH), 4.15–4.03 (1H, m, C*H*(CH$_2$)$_2$), 4.00–3.90 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.79 (1H, dd, *J* 11.2, 4.4, CHC*H*HOH), 3.74 (1H, dd, *J* 11.2, 6.2, CHCH*H*OH), 3.57 (1H, dd, *J* 10.9, 3.8, CH$_2$CHC*H*HOH), 3.51 (1H, dd, *J* 10.9, 5.0, CH$_2$CHCH*H*OH), 2.79 (2H, d, *J* 7.3, C*H*$_2$CHCH$_2$OH), 1.83–1.871 (4H, m, alkyl-*H*), 1.60–1.10 (28H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 159.0 (Ar–*C*), 158.2 (Ar–*C*), 130.8 (Ar–*C*), 130.3 (Ar–CH), 129.5 (Ar–*C*), 127.7 (Ar–CH), 115.1 (Ar–CH), 115.0 (Ar–CH), 68.2 (OCH$_2$), 66.3 (CHCH$_2$OH), 63.9 (CH$_2$CHCH$_2$OH), 55.7 (CHCH$_2$OH), 53.3 (CH(CH$_2$)$_2$), 50.1 (*C*(CH$_3$)$_2$), 36.0 (CH$_2$CHCH$_2$OH), 29.1 (alkyl-CH$_2$), 29.1 (alkyl-CH$_2$), 29.0 (alkyl-CH$_2$), 28.9 (alkyl-CH$_2$) (plus six overlapping peaks), 28.8 (alkyl-CH$_2$), 28.7 (alkyl-CH$_2$), 25.9 (alkyl-CH$_2$), 25.7 (alkyl-CH$_2$), 24.2 (CH$_3$), 23.2 (CH$_3$′); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{57}N_2O_6$ 625.4211, found 625.4205.

*4.1.13. Macrocycle **17**.* Thionyl chloride (2.00 mL, 27.0 mmol) was added to a stirring suspension of macrocycle **2** (1.42 g, 2.27 mmol) in DCM (50 mL). The resulting mixture was stirred at RT for 23 h, then concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM/ethyl acetate) to yield the title compound **17** (1.43 g, 94%) as a white solid. Mp 145–148 °C; R_f 0.25 (49:1 DCM/ethyl acetate); $[\alpha]_D^{21}$ +37.9 (*c* 0.58, $CHCl_3$); ν_{max}/cm^{-1} 3376 (NH), 2924 (CH), 2854 (CH), 1652 (C=O), 1612 (Ar C=C), 1584 (NH), 1510 (N–C=O), 1471 (Ar C=C), 1240 (C–O–C), 1179 (Ar CH), 1033 (C–O–C), 836 (Ar CH), 749 (C–Cl); δ_H (400 MHz, $CDCl_3$) 7.17–7.10 (4H, m, Ar–*H*), 7.08 (1H, d, *J* 7.6, N*H*), 6.94–6.71 (4H, m, Ar–*H*), 6.47 (1H, d, *J* 8.2, N*H*), 5.17–5.09 (1H, m, C*H*CH$_2$Cl), 4.37–4.22 (1H, m, C*H*(CH$_2$)$_2$), 4.04–3.87 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.75 (2H, d, *J* 5.6, CHCH$_2$Cl), 3.44 (1H, dd, *J* 11.4, 3.5, CH$_2$CHC*H*HCl), 3.38 (1H, dd, *J* 11.4, 4.4, CH$_2$CHCH*H*Cl), 2.87 (1H, dd, *J* 13.5, 5.9, C*H*HCHCH$_2$Cl), 2.79 (1H, dd, *J* 13.5, 8.8, CH*H*CHCH$_2$Cl), 1.87–1.66 (4H, m, alkyl-*H*), 1.57–1.25 (28H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 173.3 (*C*=O), 172.3 (*C*=O), 158.9 (Ar–*C*), 158.2 (Ar–*C*), 130.2 (Ar–*C*), 130.1 (Ar–CH), 128.4 (Ar–*C*), 127.6 (Ar–CH), 114.9 (Ar–CH), 114.8 (Ar–CH), 67.9 (OCH$_2$), 67.8 (OCH$_2$′), 53.6 (CHCH$_2$Cl), 51.5 (CH(CH$_2$)$_2$), 49.8 (*C*(CH$_3$)$_2$), 47.2 (CHCH$_2$Cl), 45.9 (CH$_2$CHCH$_2$Cl), 36.2 (CH$_2$CHCH$_2$Cl), 29.2 (alkyl-CH$_2$), 29.1 (alkyl-CH$_2$), 29.1 (alkyl-CH$_2$), 28.9 (alkyl-CH$_2$), 28.8 (alkyl-CH$_2$) (plus six overlapping peaks), 25.8 (alkyl-CH$_2$), 25.7 (alkyl-CH$_2$), 24.6 (CH$_3$), 22.3 (CH$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{55}{}^{35}Cl_2N_2O_4$ 661.3533, found 661.3533.

*4.1.14. Macrocycle **1**.* Tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 7.60 mL, 7.60 mmol) was added to a stirring solution of macrocycle **17** (1.25 g, 1.89 mmol) in DCM (100 mL). The resulting mixture was stirred at RT for 43 h. The mixture was concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with satd aq sodium citrate (3×100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:1 hexane/ethyl acetate, 0.4% Et_3N) to yield the title compound **1** (0.57 g, 51%) as a white gum. Mp 62–65 °C; R_f 0.18 (1:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ −45.4 (*c* 0.44, $CHCl_3$); ν_{max}/cm^{-1} 2926 (CH), 2855 (CH), 1656 (C=N), 1612 (Ar C=C), 1583 (Ar C=C), 1512 (Ar C=C), 1472 (Ar C=C), 1247 (C–O–C), 1116 (C–O–C), 831 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.19–7.08 (4H, m, Ar–*H*), 6.87–6.82 (4H, m, Ar–*H*), 5.12 (1H, dd, *J* 10.0, 6.5, H-5), 4.55 (1H, dd,

J 10.0, 8.5, H-4a), 4.51–4.43 (1H, m, H-30), 4.23 (1H, dd, *J* 9.4, 8.5, H-31a), 4.14 (1H, dd, *J* 8.5, 6.5, H-4b), 4.04 (1H, dd, *J* 8.5, 7.2, H-31b), 3.97 (4H, t, *J* 6.5, OCH_2, OCH_2'), 3.09 (1H, dd, *J* 13.8, 5.0, H-29a), 2.69 (1H, dd, *J* 13.8, 8.2, H-29b), 1.83–1.73 (4H, m, alkyl-*H*), 1.60 (3H, s, CH_3), 1.59 (3H, s, CH_3'), 1.54–1.26 (22H, m, alkyl-*H*); δ_C (101 MHz, $CDCl_3$) 169.8 (N=*C*O), 169.6 (N=*C*O′), 158.5 (Ar–*C*), 157.8 (Ar–*C*), 134.8 (Ar–*C*), 130.5 (Ar–*C*H), 129.2 (Ar–*C*), 127.8 (Ar–*C*H), 114.8 (Ar–*C*H), 114.6 (Ar–*C*H), 75.7 (C-4), 71.7 (C-31), 68.9 (C-5), 68.0 (OCH_2), 67.8 (OCH_2'), 67.1 (C-30), 40.1 (C-29), 38.6 ($C(CH_3)_2$), 29.3 (alkyl-CH_2), 29.3 (alkyl-CH_2), 29.2 (alkyl-CH_2), 29.1 (alkyl-CH_2), 29.1 (alkyl-CH_2), 29.0 (alkyl-CH_2), 29.0 (alkyl-CH_2), 29.0 (alkyl-CH_2) (plus four overlapping peaks), 25.9 (alkyl-CH_2), 24.6 (CH_3), 23.6 (CH_3'); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{53}N_2O_4$ 589.4000, found 589.3987.

The following three-step procedure forms C_1-Box ligand **20** via **35** and **36**.

*4.1.15. N^1-((S)-2-Hydroxy-1-phenylethyl)-N^3-((R)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide (**35**).* A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbo diimide hydrochloride (EDCI) (84.1 mg, 4.39 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirring solution of (*S*)-3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid **33** (99.9 mg, 3.97 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (62.6 mg, 4.63 mmol) and Et_3N (1.40 mL, 10.0 mmol) in $CHCl_3$ (37 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. A solution of (*R*)-2-amino-3-phenylpropan-1-ol (66.2 mg, 4.38 mmol) in $CHCl_3$ (7 mL) was added dropwise. The resulting solution was warmed to RT and stirred for 41 h. The reaction was quenched with 3 M aq HCl (12 mL) and the aqueous layer extracted with $CHCl_3$. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 ethyl acetate/petrol ether) to yield the title compound **35** (1.05 g, 69%) as a pale yellow solid. Mp 119–122 °C; R_f 0.30 (9:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +54.9 (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} 3315 (OH/NH), 3275 (OH/NH), 3062 (Ar CH), 2942 (CH), 1633 (C=O), 1523 (N–C=O), 1495 (Ar C=C), 1453 (Ar C=C), 1285 (C–N), 1056 (C–OH), 1032 (C–OH), 911 (Ar CH), 735 (Ar CH), 698 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.38–7.15 (11H, m, Ar–*H*, N*H*), 6.67 (1H, d, *J* 8.1, N*H*), 5.07–4.93 (1H, m, *CH*CH_2OH), 4.23–4.06 (1H, m, *CH*CH_2OH′), 3.85 (1H, dd, *J* 11.4, 4.0, CHC*H*HOH), 3.77 (1H, dd, *J* 11.7, 6.6, CHC*H*HOH′), 3.63 (1H, dd, *J* 11.7, 4.0, CHCH*H*OH′), 3.54 (1H, dd, *J* 11.4, 5.1, CHCH*H*OH), 2.89 (1H, dd, *J* 13.6, 6.6, *CH*HCHCH_2), 2.80 (2H, dd, *J* 13.6, 7.7, CH*H*CHCH_2), 1.41 (3H, s, CH_3), 1.35 (3H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 174.0 (*C*), 173.8 (*C*), 138.8 (*C*), 137.5 (*C*), 129.2 (*C*H), 128.8 (*C*H), 128.5 (*C*H), 127.8 (*C*H), 126.6 (*C*H), 126.5 (*C*H), 66.0 (CH_2), 63.9 (CH_2), 55.8 (*C*H), 53.2 (*C*H), 49.8 (*C*), 36.7 (CH_2), 23.6 (CH_3), 23.5 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{29}N_2O_4$ 385.2122, found 385.2122.

*4.1.16. N^1-((S)-2-Chloro-1-phenylethyl)-N^3-((R)-1-chloro-3-phenyl propan-2-yl)-2,2-dimethylmalonamide (**36**).* Thionyl chloride (1.60 mL, 21.9 mmol) was added to a stirring suspension of N^1-((*S*)-2-hydroxy-1-phenylethyl)-N^3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **35** (74.0 mg, 1.92 mmol) in DCM (40 mL). The resulting mixture was stirred at RT for 19 h, then concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM/ethyl acetate) to yield the title compound **36** (0.681 g, 85%) as a white solid. Mp 157–160 °C; R_f 0.64 (49:1 DCM/ethyl acetate); $[\alpha]_D^{21}$ +42.3 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1} 3310 (NH), 3063 (Ar CH), 3028 (Ar CH), 2972 (CH), 1637 (C=O), 1554 (N–C=O), 1526 (N–C=O), 1496 (Ar C=C), 1455 (Ar C=C), 699 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.43–7.22 (11H, m, Ar–*H*, N*H*), 6.68 (1H, d, *J* 8.1, N*H*), 5.33–5.25 (1H, m, *CH*CH_2Cl), 4.46 (1H, tdd, *J* 7.7, 4.4, 3.7, CH_2*CH*CH_2Cl), 3.85 (1H, dd, *J* 11.4, 5.1, CHC*H*HCl), 3.78 (1H, dd, *J* 11.4, 6.2, CHCH*H*Cl), 3.60 (1H, dd, *J* 11.4, 4.4, CH_2CHC*H*HCl), 3.51 (1H, dd, *J* 11.4, 3.7, CH_2CHCH*H*Cl), 2.95 (2H, d, *J* 7.7, CH_2CHCH_2Cl), 1.50 (3H, s, CH_3), 1.45 (3H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 173.3 (*C*), 172.8 (*C*), 138.3 (*C*), 136.7 (*C*), 129.2 (*C*H), 128.9 (*C*H), 128.8 (*C*H), 128.2 (*C*H), 127.0 (*C*H), 126.5 (*C*H), 54.1 (CH_2), 51.1 (CH_2), 49.5 (*C*), 47.5 (*C*H), 46.3 (*C*H), 37.4 (CH_2), 24.0 (CH_3), 23.7 (CH_3); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}{}^{35}Cl_2N_2O_2$ 421.1444, found 421.1442.

*4.1.17. (R)-4-Benzyl-2-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl) propan-2-yl)-4,5-dihydrooxazole (**20**).* TBAF (1.0 M in THF, 5.50 mL, 5.50 mmol) was added to a stirring solution of N^1-((*S*)-2-chloro-1-phenylethyl)-N^3-((*R*)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **36** (56.3 mg, 1.34 mmol) in THF (50 mL). The resulting mixture was stirred at RT for 18 h, concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with satd aq sodium citrate (3×100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:3 hexane/ethyl acetate, 0.4% Et_3N) to yield the title compound **20** (36.2 mg, 80%) as a colourless oil. R_f 0.10 (3:7 hexane/ethyl acetate); $[\alpha]_D^{20}$ −51.9 (*c* 1.31, $CHCl_3$); ν_{max}/cm^{-1} 3059 (Ar CH), 3028 (Ar CH), 2984 (CH), 2936 (CH), 2901 (CH), 1651 (N=C), 1604 (Ar C=C), 1495 (Ar C=C), 1455 (Ar C=C), 1145 (C–O), 1116 (C–O), 979 (C–N), 921 (Ar CH), 756 (Ar CH), 700 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (10H, m, Ar–*H*), 5.22 (1H, dd, *J* 9.9, 7.7, OCH_2*CH*N), 4.65 (1H, dd, *J* 10.1, 8.3, OC*H*HCHN′), 4.54–4.41 (1H, m, OCH_2*CH*N′), 4.26 (1H, dd, *J* 9.9, 8.8, OC*H*HCHN), 4.18–4.03 (2H, m, OCH*H*CHN, OCH*H*CHN′), 3.16 (1H, dd, *J* 13.8, 5.0, ArC*H*HCH), 2.72 (1H, dd, *J* 13.8, 8.6, ArCH*H*CH), 1.63 (3H, s, CH_3), 1.59 (3H, s, CH_3'); δ_C (75 MHz, $CDCl_3$) 170.3 (*C*), 169.4 (*C*), 142.5 (*C*), 137.7 (*C*), 129.5 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 127.6 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 75.5 (CH_2), 72.1 (CH_2), 69.5 (*C*H), 67.1 (*C*H), 41.4 (CH_2), 38.7 (*C*), 24.4 (2×CH_3 overlapping); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_2$ 349.1911, found 349.1908.

*4.1.18. Prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate (**29**).* EDCI (1.98 g, 10.3 mmol) was added to a solution of propargyl alcohol (0.600 mL, 10.3 mmol) and 3,3,3-tris(4-chlorophenyl)propionic acid (4.03 g, 9.93 mmol) in DCM (100 mL). 4-(Dimethylamino) pyridine (DMAP) (13.3 mg, 1.09 mmol) was added and the resulting mixture was stirred at RT for 5 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 hexane/ethyl acetate) to yield the title compound **29** (3.83 g, 83%) as a white solid. Mp 88–89 °C; R_f 0.55 (4:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3290 (≡CH), 3282 (≡CH), 3075 (Ar CH), 2948 (CH), 2129 (C≡C), 1729 (C=O), 1589 (Ar C=C), 1490 (Ar C=C), 1441 (Ar C=C), 1269 (≡CH), 1219 (Ar CH), 1137 (C–O), 1093 (Ar C–Cl), 803 (Ar CH), 688 (≡CH); δ_H (400 MHz, C_2D_6O) 7.28–7.08 (6H, m, Ar–*H*), 7.12–6.94 (6H, m, Ar–*H*), 4.36 (2H, d, *J* 2.5, CH_2C≡CH), 3.61 (2H, s, CH_2COO), 2.33 (1H, t, *J* 2.5, ≡C*H*); δ_C (101 MHz, $C_3D_6O_2$) 169.4 (*C*), 143.9 (*C*), 132.7 (*C*), 130.3 (CH), 128.3 (CH), 77.2 (CH), 74.9 (*C*), 54.6 (*C*), 52.0 (CH_2), 45.8 (CH_2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{17}{}^{35}Cl_3NaO_2$ 465.0186, found 465.0183.

*4.1.19. 3-Bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate (**22**).* Silver nitrate (28.8 g, 1.69 mmol) was added to a stirring suspension of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **29** (2.00 g, 4.51 mmol) and NBS (90.0 mg, 5.06 mmol) in acetone (50 mL). The flask was protected from light and the mixture stirred at RT for 1 h. The reaction was diluted with petrol ether (50 mL) and washed with water. The aqueous layer was extracted with 1:1 petrol ether/diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **22** (2.5 g, 100%) as a white solid. Mp 116–188 °C; R_f 0.75

(9:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 3083 (Ar CH), 2934 (CH), 2873 (CH), 2229 (C≡C), 1748 (C=O), 1591 (Ar C=C), 1490 (Ar C=C), 1326 (C–O), 1195 (Ar CH), 1183 (Ar CH), 1137 (C–O), 1092 (Ar C–Cl), 1012 (C–Br), 817 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.34–7.23 (6H, m, Ar–*H*), 7.19–7.05 (6H, m, Ar–*H*), 4.48 (2H, s, $CH_2C{\equiv}CBr$), 3.70 (2H, s, CH_2COO); δ_C (75 MHz, $CDCl_3$) 169.4 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (*CH*), 128.3 (*CH*), 73.5 (*C*), 54.6 (*C*), 52.8 (CH_2), 47.3 (*C*), 45.7 (CH_2); HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{17}{}^{79}Br^{35}Cl_3O_2$ 520.9472, found 520.9479.

*4.1.20. 3-Hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate (**37**).* 3,3,3-Tris(4-chlorophenyl)propanoic acid (4.08 g, 12.3 mmol), DMAP (14.3 mg, 1.17 mmol) and EDCI (2.35 g, 12.3 mmol) were added sequentially to a stirring solution of propane-1,3-diol (0.810 mL, 11.2 mmol) in DCM (180 mL). The resulting mixture was stirred at RT for 22 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether/ethyl acetate to 1:1 petrol ether/ethyl acetate) to yield the title compound **37** (3.48 g, 67%) as a white solid. Mp 89–90 °C; R_f 0.05 (4:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 3401 br (OH), 3067 (Ar CH), 3032 (Ar CH), 2961 (CH), 2888 (CH), 1731 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1491 (Ar C=C), 1150 (C–O–C), 1096 (Ar C–Cl), 1053 (C–OH), 1013 (C–O–C), 811 (Ar CH), 733 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.21–7.15 (6H, m, Ar–*H*), 7.12–7.00 (6H, m, Ar–*H*), 3.90 (2H, t, *J* 6.1, OCH_2), 3.56 (2H, s, CH_2COO), 3.35 (2H, t, *J* 6.1, CH_2OH), 1.54 (3H, quin., *J* 6.1, $CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 170.6 (*C*), 144.1 (*C*), 132.7 (*C*), 130.3 (CH), 128.3 (CH), 61.6 (CH_2), 59.0 (CH_2), 54.7 (*C*), 46.1 (CH_2), 31.4 (CH_2); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{24}H_{25}{}^{35}Cl_3NO_3$ 480.0895, found 480.0885.

*4.1.21. 3-(3,3,3-Tris(4-Chlorophenyl)propanoyloxy)propyl acrylate (**25**).* Et_3N (3.80 mL, 27.3 mmol) was added to a stirring solution of 3-hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate **37** (2.73 g, 5.89 mmol) in DCM (75 mL) under an argon atmosphere. The resulting mixture was cooled to 0 °C and DMAP (70.0 mg, 0.590 mmol) and acrylolyl chloride (1.10 mL, 14.0 mmol) were added. The resulting mixture was stirred for 2 h. The reaction was quenched with water (75 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether/ethyl acetate) to yield the title compound **25** (1.77 g, 63%) as a colourless oil. R_f 0.43 (9:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 3070 (Ar CH), 3036 (=CH), 2966 (CH), 2901 (CH), 1721 (C=O), 1636 (C=C), 1619 (Ar C=C), 1590 (Ar C=C), 1490 (Ar C=C), 1185 (C–O–C), 1147 (C–O–C), 1094 (Ar C–Cl), 985 (=CH), 907 (=CH), 811 (=CH), 730 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.23–7.12 (6H, m, Ar–*H*), 7.11–6.98 (6H, m, Ar–*H*), 6.31 (1H, dd, *J* 17.6, 1.5, =C*H*H), 6.01 (1H, dd, *J* 17.6, 10.3, C*H*=CH_2), 5.74 (1H, dd, *J* 10.3, 1.5, CH*H*), 3.95 (2H, t, *J* 6.3, CH_2OCO), 3.83 (2H, t, *J* 6.3, CH_2OCO'), 3.56 (2H, s, CH_2COO), 1.67 (2H, quin., *J* 6.3, $CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 170.1 (*C*), 165.9 (*C*), 144.1 (*C*), 132.6 (*C*), 130.9 (CH_2), 130.3 (*CH*), 128.2 (*CH*), 128.1 (*CH*), 61.1 (CH_2), 60.7 (CH_2), 54.6 (*C*), 46.0 (CH_2), 27.6 (CH_2); HRMS (ESI): $[M+NH_4]^+$ calcd for $C_{27}H_{27}{}^{35}Cl_3NO_4$ 534.1000, found 534.1002.

4.2. General procedure for the Cadiot–Chodkiewicz reaction

n-Butyl lithium (1 equiv) was added dropwise to a stirring solution of 4,4′,4″-((4-(pent-4-ynyloxy)phenyl)methanetriyl) tris(-*tert*-butylbenzene) **21** (1 equiv) in THF (0.09 M) at −78 °C. The resulting mixture was warmed to 0 °C and stirred for 40 min. Copper iodide/chloride (1.3 equiv) was added and the resulting mixture warmed to RT and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of Box ligand (1 equiv) and 3-bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **22** (1 equiv) in THF (0.05 M) was added. The resulting mixture was warmed to RT and stirred until the reaction was complete. The reaction was quenched with 17.5% aq ammonia solution satd with ethylenediaminetetraacetic acid (EDTA) and stirred under air for 40 min. The aqueous layer was extracted with DCM and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^1H NMR spectroscopic analysis (Table 1). For characterization, a sample was purified by column chromatography (hexane to 9:1 hexane/ethyl acetate) to yield thread **23** as a white solid. Mp 90–94 °C; R_f 0.38 (9:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2962 (Ar CH), 2903 (CH), 2868 (CH), 2258 (C≡C), 1749 (C=O), 1606 (Ar C=C), 1505 (Ar C=C), 1492 (Ar C=C), 1248 (C–O–C), 1141 (C–O), 1096 (Ar C–Cl), 1054 (C–O–C), 824 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.28–7.23 (10H, m, Ar–*H*), 7.17–7.07 (16H, m, Ar–*H*), 6.82–6.75 (2H, m, Ar–*H*), 4.51 (2H, s, $OCH_2C{\equiv}C$), 4.05 (2H, t, *J* 6.6, OCH_2CH_2), 3.68 (2H, s, CH_2COO), 2.56 (2H, t, *J* 6.6, $CH_2C{\equiv}C$), 2.04 (2H, quin., *J* 6.6, $CH_2CH_2CH_2$), 1.32 (27H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 169.4 (*C*), 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 143.9 (*C*), 139.8 (*C*), 132.8 (*C*), 132.3 (CH), 130.7 (CH), 130.3 (CH), 128.3 (CH), 124.0 (CH), 113.0 (CH), 81.2 (*C*), 71.7 (*C*), 68.8 (*C*), 65.8 (CH_2), 64.7 (*C*), 63.1 (*C*), 54.6 (*C*), 52.6 (CH_2), 45.8 (CH_2), 34.3 (*C*), 31.6 (CH_3), 22.7 (CH_2), 14.1 (CH_2); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{66}H_{69}{}^{35}Cl_3NO_3$ 1028.4338, found 1028.4340.

Thread **24** was also isolated from the reaction as a white solid. Mp 84–88 °C; R_f 0.14 (9:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 3075 (Ar CH), 3040 (Ar CH), 2932 (CH), 2254 (C≡C), 1747 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1490 (Ar C=C), 1369 (CH), 1193 (Ar CH), 1138 (C–O), 1094 (Ar C–Cl), 808 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.34–7.22 (12H, m, Ar–*H*), 7.20–7.09 (12H, m, Ar–*H*), 4.54 (4H, s, $CH_2C{\equiv}C$), 3.71 (4H, s, CH_2COO); δ_C (75 MHz, $CDCl_3$) 169.3 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (CH), 128.4 (CH), 73.2 (*C*), 70.3 (*C*), 54.6 (*C*), 52.3 (CH_2), 45.7 (CH_2); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{48}H_{36}{}^{35}Cl_6NO_4$ 900.0770, found 900.0773.

4.3. General procedure for the oxidative Heck reaction

A solution of palladium(II) acetate (20 mol %) and Box ligand (1 equiv) in DMF (0.05 M) was stirred at RT for 2.5 h. A solution of 3-(3,3,3-tris(4-chlorophenyl)propanoyloxy)propyl acrylate **25** (1 equiv), 4-(3-(4-(tris(4-*tert*-butyl-phenyl)methyl)phenoxy) propoxy)phenylboronic acid **26** (3 equiv) and benzoquinone (1 equiv) in $CHCl_3$ (0.05 M) was added. The resulting mixture was placed under an oxygen atmosphere and heated to 25 °C for 48 h. The reaction was diluted with DCM, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^1H NMR analysis (Table 2). For characterization, a sample was purified by column chromatography (19:1 petrol ether/ethyl acetate to 9:1 petrol ether/ethyl acetate) to yield thread **27** as a white solid. Mp 164–166 °C; R_f 0.16 (9:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 2961 (Ar CH), 2905 (CH), 2868 (CH), 1738 (C=O), 1713 (C=O), 1634 (C=C), 1604 (Ar C=C), 1506 (Ar C=C), 1492 (Ar C=C), 1473 (Ar C=C), 1246 (C–O–C), 1165 (C–O), 1096 (Ar C–Cl), 1055 (C–O–C), 826 (Ar CH); δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 15.6, C*H*=CH), 7.47 (2H, s, Ar–*H*), 7.31–7.23 (13H, m, Ar–*H*), 7.17–7.09 (13H, m, Ar–*H*), 6.97–6.91 (2H, m, Ar–*H*), 6.84–6.78 (2H, m, Ar–*H*), 6.31 (1H, d, *J* 15.6, OCOC*H*=CH), 4.23 (2H, t, *J* 6.2, CH_2O), 4.20–4.09 (4H, m, CH_2OCO, CH_2O'), 3.99 (2H, t, *J* 6.2, CH_2OCO'), 3.67 (2H, s, CH_2COO), 2.30 (2H, quin., *J* 6.2, $CH_2CH_2CH_2$), 1.82 (2H, quin., *J* 6.2, $CH_2CH_2CH_2'$), 1.33 (27H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 170.2 (*C*), 167.1 (*C*), 160.8 (*C*), 156.6 (*C*), 148.3 (*C*), 144.8 (*C*), 144.2 (CH), 139.8 (*C*), 132.7 (*C*), 132.3 (CH), 130.7 (CH), 130.3 (CH), 129.8 (CH), 128.3 (CH), 127.0 (*C*), 124.1 (CH), 115.2 (CH), 114.9 (CH), 113.0 (CH), 64.7 (CH_2), 64.0 (CH_2), 63.1 (*C*), 61.4 (CH_2), 60.7 (CH_2), 54.6 (*C*), 46.1 (CH_2), 34.3 (*C*), 31.4 (CH_3), 29.3 (CH_2), 27.8 (CH_2); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{73}H_{79}{}^{35}Cl_3NO_6$ 1170.4967, found 1170.4984.

4.4. General procedure for the CuAAC click reaction

A solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (1 equiv) and Box ligand (1 equiv) in DCM (1 mL) was stirred for 2.5 h. A solution of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **29** (1 equiv) and 4,4′,4″-((4-(3-azido-propoxy) phenyl) methanetriyl)tris(*tert*-butylbenzene) **30** (1 equiv) in DCM (1.5 mL) was added. The resulting mixture was concentrated under reduced pressure to the required concentration and the reaction mixture heated to 25 °C until the reaction was complete. The resulting mixture was diluted with DCM, washed with 17.5% aq NH_3 satd with EDTA, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by ^{1}H NMR analysis (Table 3). For characterization, a sample was purified by column chromatography (4:1 petrol ether/ethyl acetate to ethyl acetate) to yield thread **31** as a white solid. Mp 129–131 °C; R_f 0.14 (4:1 petrol ether/ethyl acetate); ν_{max}/cm^{-1} 2961 (Ar CH), 2903 (CH), 2868 (CH), 1739 (C=O), 1505 (Ar C=C), 1492 (Ar C=C), 1401 (N=N), 1363 (N=N), 1245 (C–O–C), 1185 (C–O–C), 1146 (C–O–C), 1110 (C–N), 1096 (Ar C–Cl), 1055 (C–O–C), 822 (Ar CH); δ_H (300 MHz, $CDCl_3$) 7.28–7.19 (14H, m, Ar–*H*), 7.15–7.06 (15H, m, Ar–*H*, C=C*H*N), 6.81–6.72 (2H, m, Ar–*H*), 5.00 (2H, s, O*CH*$_2$C=C), 4.58 (2H, t, *J* 6.3, NC*H*$_2$), 3.96 (2H, t, *J* 6.3, OC*H*$_2$CH$_2$), 3.68 (2H, s, *CH*$_2$COO), 2.38 (2H, quin., *J* 6.3, CH$_2$*CH*$_2$CH$_2$), 1.33 (27H, s, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.2 (*C*), 156.2 (*C*), 148.4 (*C*), 144.1 (*C*), 144.0 (*C*), 142.1 (*C*), 140.2 (*C*), 132.6 (*CH*), 132.4 (*C*), 130.7 (*CH*), 130.3 (*CH*), 128.2 (*CH*), 124.1 (*CH*), 112.9 (*CH*), 63.8 (*C*), 63.1 (*CH*$_2$), 57.8 (*CH*$_2$), 54.5 (*C*), 47.3 (*CH*$_2$), 46.0 (*CH*$_2$), 34.3 (*C*), 31.4 (*CH*$_3$), 30.0 (*CH*$_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{64}H_{67}{}^{35}Cl_3N_3O_3$ 1030.4243, found 1030.4244.

Acknowledgements

We would like to thank EPSRC (EP/G006695/1) funding and the EPSRC Mass Spectrometry services at Swansea for analytical support.

Supplementary data

Supplementary data available: copies of ^{1}H NMR and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.069.

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